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DISSOLUTION OF PHOSPHATIC URINARY CALCULI BY THE RETROGRADE INTRODUCTION OF A CITRATE SOLUTION CONTAINING MAGNESIUM*

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BOSTON

IN a previous communication[1] from this clinic the possibility of using an isotonic citrate solution at a pH of 4.0 to dissolve urinary calculi was discussed and the successful treatment of one case of bladder stones by this method was reported. It soon became apparent that this solution was too irritating for routine clinical use; it is perhaps of historical interest that the patient who had been successfully treated for bladder stones had a so-called "cord bladder" and hence was not disturbed by the irritation. Furthermore, if citrate solutions by irritation give rise to bleeding, this continues since the citrate prevents coagulation of blood. A study was therefore undertaken to find a solution that would be not only effective in dissolving calculi but less irritating.

The speed with which various solutions dissolve calcium phosphate calculi was quantitated by the speed with which they decalcified rabbits' teeth[2]; the irritability of the solutions was studied by noting their effect on the mucosa of rabbits' bladders.[3] A large number of organic acids were tried; the effect of pH, tonicity, temperature, pK of the calcium salt of the acid and so forth were studied; some of the underlying laws were formulated[4]; and finally an isotonic solution of levulinic acid at a pH of 4.0 was selected. This solution was found to be less irritating, albeit considerably less effective, than the original citrate solution. The net result was an improvement, however, and several successful clinical experiences were obtained.

At this juncture it was discovered that the addition of magnesium ions markedly reduced the irritability of levulinic solutions[3]; the same was found to be true for citrate solutions and they were once more taken up for clinical use. The present paper is concerned with a report of the dissolution of phosphatic stones in patients in whom a citrate solution containing magnesium ions (Solution G§) was employed.

CLINICAL MANAGEMENT OF CASES

Infection

In most cases during the dissolution the patients received moderate doses of sulfathiazole or a similar drug to prevent infection if it was not present, or to reduce it if already present.

Apparatus

The main object, of course, is to keep the solution in contact with the stone as much as possible. The actual apparatus used in each case depended on whether one was working through a simple nephrostomy tube, a two-way nephrostomy tube, two nephrostomy tubes, a ureteral catheter and a nephrostomy tube, or one or more ureteral catheters; technical aspects also varied depending on the degree of patency of the ureter and on how irritable the bladder and urethra were. Solution G is somewhat irritating, and some patients developed bladder symptoms if the solution was allowed to come out through the bladder, whereas others did not. Cases 3 and 5 illustrate how this difficulty was overcome.

When the stones lie in the kidney calyxes it is desirable that a slight amount of intrapelvic pressure be obtained to make sure that the solution gets around all the stones. However, the operator should see to it that this pressure is not continuous lest a constant back pressure stir up a pyelonephritis. This means that the solution must in some way be introduced intermittently. Figure

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§The formula of Solution G is as follows:

Citric acid (monohydrated)	32.25 gm.
Magnesium oxide (anhydrous)	3.84 gm.
Sodium carbonate (anhydrous)	4.37 gm.
Water q. s. ad	1000 cc.

1 illustrates one possible apparatus to obtain these ends.

With rare exceptions it is better that the fluid should not go in and out of one tube, as in the Munro[5] tidal-drainage apparatus devised for irrigating so-called "cord bladders." The objection to such an apparatus arises from the fact that the dead space in the tubes is so great in comparison with the cavity being irrigated that a large proportion of the fluid that comes out of the cavity goes back into it again. The efficacy of such a system depends on the ratio of the volume of the viscus being irrigated to the volume of the dead space (tidal fluid). The Munro apparatus is very satisfactory for bladders but not for kidney pelves. If one cannot have a two-way drainage, as for example, when one is working through a ureteral catheter, it is necessary to inject the solution manually into the end of the catheter or to use the alternate apparatus, devised by our colleague, Dr. Lawrence Kinsell, and shown in Figure 2. With the latter the constant presence of an attendant is required; this attendant can, however, be the patient himself.

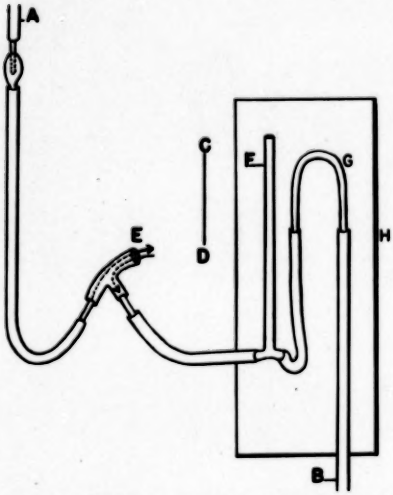

FIGURE 1. *Tidal-Drainage Apparatus to Produce Intermittent Intrapelvic Pressure through a Two-Way Nephrostomy Tube.*

A — tube from reservoir of fluid leading to Murphy drip; B — tube leading to waste-fluid; C — level where siphoning begins; D — level of pelvis; E — two-way nephrostomy tube leading to kidney pelvis; F — upright glass tube open at upper end; G — curved glass tube acting as siphon; H — board to which apparatus is fixed.

As fluid enters the system from A, the pressure rises until the fluid reaches C, the height of the siphon; at that point, fluid siphons off until air coming into tube F breaks siphon; the whole process then starts over again. The distance, C to D, measures the extent of intrapelvic pressure before the fluid siphons off.

If one is dependent entirely on the ureter for the introduction of the fluid, it is preferable to use a soft-rubber catheter (Bardam No. 10) because of the danger of erosion of the ureter after prolonged intubation with a hard-woven catheter. This soft catheter can best be introduced with the help of a fiber stylet; once in position it can be left for weeks (Case 6) or months, if one is to judge by experience with ordinary skin ureterostomies. The problem of keeping the ureteral catheter in place is a somewhat difficult one because of the tendency of the peristalsis of the ureter to displace it. This trouble has been overcome by the apparatus shown in Figure 2.

Evaluation of Results

For following the progress of dissolution and for determining just where the stone is in relation to the pelvis of the kidney, and hence whether fluid can be made to come in contact with the stone, an air pyelogram is most helpful (Fig. 5*A* and *B*). Air is preferred to a radio-opaque substance because it does not obscure the stone.

Determination of Chemical Composition of Stones

Before attempting to dissolve a stone with Solution G it is, of course, necessary to know that one is dealing with a phosphatic stone. By a "phosphatic stone" is meant one composed of calcium phosphate with or without calcium carbonate or magnesium ammonium phosphate or both. In this clinic, to the present date, no attempt has been made to separate out the various subgroups of phosphatic stones. The composition can be determined by chemical analysis if a stone has been removed in the past, by circumstantial evidence[1] or by the x-ray appearance of the stone. This last method of analysis is most useful and has already been discussed[1]; it will be taken up in more detail in another publication.[6]

Clinical Results

Solution G has been used on approximately 20 patients. In this report 7 cases are presented. These have been selected to bring out certain points.

Case Reports

CASE 1. *(Long history of recurring bilateral calcium phosphate stones; etiology of first stones probably hypercalcuria from immobilization and resulting atrophy of disuse; ingestion of milk and of calcium gluconate were added factors; stones on right dissolved with Solution G through nephrostomy tube.)*

In 1928, W. L. (No. 70740), at the age of 18, fractured his left femur and humerus. Because of nonunion he was immobilized in bed for 6 months and given large amounts of milk and calcium gluconate by mouth. Bilateral renal stones developed, for which there was adequate reason. (Immobilization alone produces marked hypercalcuria; to this was added a very high calcium intake from the milk and the calcium gluconate. The fallacy of this procedure lay in the fact that there was no point in giving a high calcium intake since nonunion of fractures is due to lack of formation of a callus, not to lack of calcification of a callus.) Left pyelolithotomy was performed but *the stone was not analyzed.* Nine years later the patient again entered the hospital with bilateral stones; a right

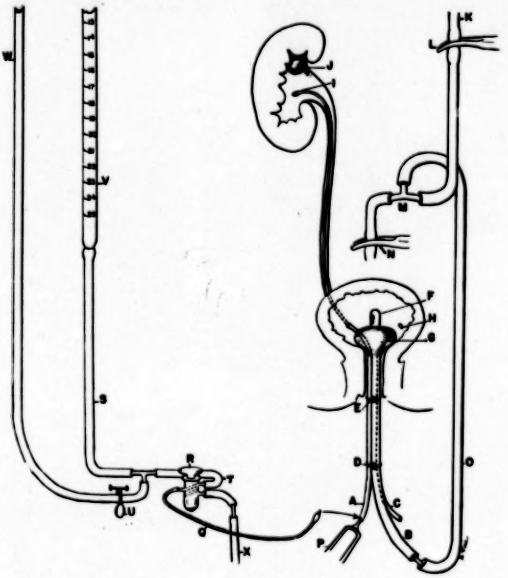

FIGURE 2. *Apparatus If Dissolution Is to Be Carried Out through One Ureteral Catheter.*

A — *ureteral catheter;* B — *proximal end of Foley catheter;* C — *tube through which balloon of Foley catheter is inflated;* D *and* E — *sutures fixing ureteral catheter to Foley catheter;* F — *distal end of Foley catheter;* G — *balloon of Foley catheter;* H — *ureteral orifice;* I — *distal end of ureteral catheter;* J — *stone;* K — *tube leading to reservoir of fluid used in bladder irrigation;* L — *forceps;* M — *glass T tube;* N — *forceps on tube leading to waste-fluid bottle;* O — *rubber tubing;* P — *syringe through which Solution G is inserted;* Q — *small-caliber tubing similar to ureteral catheter;* R — *three-way stopcock;* S — *tube leading to burette;* T — *rubber tubing;* U — *clamp;* V — *burette;* W — *end of tube leading to Solution G;* X — *tube leading to waste bottle.*

Since it is very irritating to void around a catheter it is necessary to have a bladder catheter as well as a ureteral catheter. A Foley catheter is used since it can be drawn tightly into the bladder neck and thus securely fixed. In this way a fixed object is furnished to which the ureteral catheter can be sewn. To irrigate the bladder one clamps the tube at N *and opens the tube at* L, *thus allowing fluid to go into the bladder; to empty the bladder one opens the tube at* N *and clamps the tube at* L.

If the patient is to work the apparatus himself, it is suggested that the apparatus at the left of the diagram be used instead of a syringe. The patient fills the burette to the desired level by opening the clamp U. *To put fluid into the kidney tube, the burette is connected through tubes* S *and* T *with the small tube* Q, *by adjusting the three-way stopcock* R. *To let fluid out of the kidney, tube* Q *is connected with tube* X *by turning stopcock* R. *If a No. 10 Bardam tube is used for the ureteral catheter and for tube* Q, *the dead space amounts to 3 cc. for 125 cm. of tubing.*

nephrolithotomy and a right nephrostomy were performed. When the present studies were started he had been wearing a nephrostomy tube for 4 years and some large stones

burning on urination. At the end of 10 days the stones were definitely smaller (Fig. 3*B*). Each week thereafter showed further improvement until the stones were entirely

FIGURE 3. *Roentgenograms in* ***Case 1 before*** **(A),** *during* (B *and* C) *and after* (D) *Dissolution of Stones.*

In B, *note that the small stone above the catheter has entirely disappeared and that the large stones below the catheter are much smaller; in* D, *note that the small residual shadow indicated by the arrow lies outside of the kidney pelvis, since air in the lower calyx does not extend to the shadow.*

had formed in the right kidney (Fig. 3*A*). The serum calcium and phosphorus values were normal; the urine showed *Proteus vulgaris* on culture, which was probably the cause of the recurrent stone.

Solution G was introduced through the nephrostomy tube and allowed to pass out through the ureter, bladder and urethra. The solution ran approximately 9 hours a day between 7 a.m. and 7 p.m. The patient used in the neighborhood of 3000 cc. daily and did not experience

dissolved (Fig. 3*C* and 3*D*). The entire procedure took approximately 3 months; thereafter the nephrostomy tube was removed. During the time of irrigation the patient received 0.5 gm. of sulfathiazole three times daily. He was followed in the Out Patient Department for 1 year. At the end of that time *P. vulgaris* infection was no longer present; the urine contained some colon bacilli but was acid; a pyelogram showed no recurrence, and the patient resumed his work as a radio engineer.

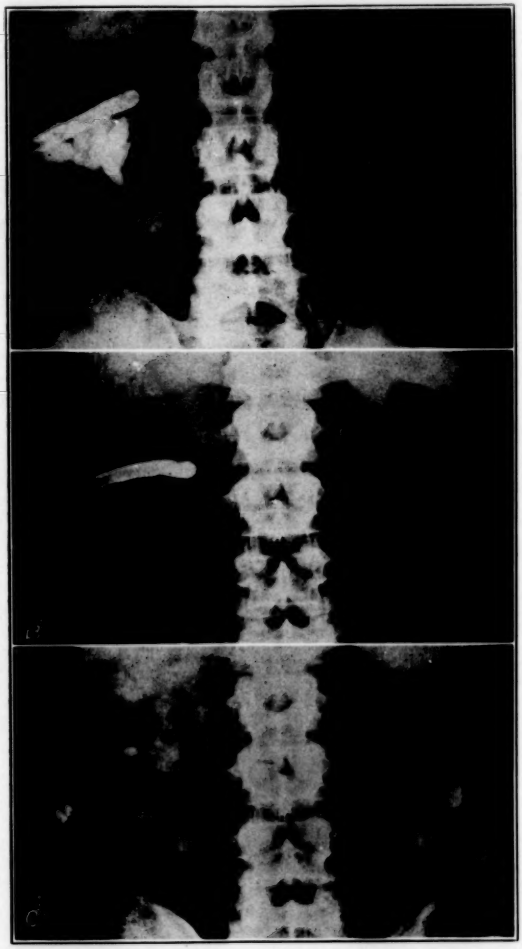

FIGURE 4. *Roentgenograms in Case 2 before* (A), *during* (B) *and after* (C) *Attempted Dissolution.*

Note that the stones which dissolved did so completely and that those that did not dissolve remained as they were, because of lack of contact with the solution.

CASE 2. *(A man with a long history of recurring bilateral calcium phosphate stones; many operations; etiology of original stones obscure, possibly kinked ureters; more recent etiology infection with urea-splitting organisms; dissolution with Solution G through bilateral two-way nephrostomy tubes of those stones in contact with kidney pelves.)*

J. S. (No. 308796), in 1925, at the age of 17, developed stones in the left kidney, for which a left nephrolithotomy was performed. In 1937, bilateral stones were found; in 1938 a right nephrolithotomy and a right nephrostomy were performed, and in 1939 a left nephrolithotomy and a left nephrostomy. The patient was referred to the Massachusetts General Hospital by Dr. Leo E. Gibson of Syracuse, New York.

The serum calcium and phosphorus levels were normal; the urine was constantly alkaline and contained *Escherichia coli* and a nonhemolytic streptococcus; the analysis of a stone that had been removed previously showed it to be pure calcium phosphate. Large bilateral stones were present (Fig. 4*A*). As the ureters were practically nonpatent, it was impossible to use them for draining out the solution; consequently the nephrostomy tubes were connected to a modified Munro tidal-drainage system. This was without effect because of the large amount of dead space (see above). Therefore the simple nephrostomy tubes were replaced with two-way nephrostomy tubes and Solution G was allowed to run into one side and out the other (Fig. 1). The patient ran approximately 1500 cc. of the solution through each tube daily. Figure 4*B* and *C* shows the dissolution of the stones that were in contact with the kidney pelves. Figure 5*A* and *B* shows the advantage of an air pyelogram for demonstrating the relation of the stones to the kidney pelvis. Unfortunately complete contact with the stones could not be made (Fig. 5*B*), so that the patient was discharged with a few fragments still remaining and sent back to work with nephrostomy tubes left in place.

CASE 3. *(Attempted dissolution with Solution G through a nephrostomy tube of a stone not found at operation; difficulty with bladder irritability, which was finally overcome.)*

J. D. (No. 236588), a 41-year-old man, entered with two stones in the left kidney pelvis and congenital absence of the right kidney. The serum calcium and phosphorus values were normal; the blood nonprotein nitrogen was slightly elevated. A left pyelolithotomy was performed but only one stone was found; accordingly a nephrostomy tube was left in place. An analysis of the removed stone showed it to be calcium phosphate. Two weeks after the operation Solution G was introduced into the pelvis through a nephrostomy tube at the rate of 40 to 60 drops per minute, but caused marked irritability when it reached the bladder. The patient was then cystoscoped and a soft-rubber ureteral catheter was passed to the kidney pelvis; Solution G was then introduced into this catheter and allowed to come out the nephrostomy tube. The stone was readily dissolved (Fig. 6*A*, *B* and *C*).

FIGURE 5. *Further Roentgenograms in Case 2 to Show the Advantage of an Air Pyelogram (B) over a Pyelogram with Opaque Substance (A).*

In B, note that the air does not extend down to the stone in the left lower quadrant of the picture but merely goes as far as the arrow; in C, which shows the stones after attempted dissolution, note that this stone remains undissolved.

CASE 4. *(Recurrent stones due to hyperparathyroidism; removal of parathyroid tumor, leaving residual stone in right kidney; stone stationary in size for a long period of time; then rapid growth following infection with* P. vulgaris *(B. proteus); dissolution of calcium phosphate cortex, with no change in calcium oxalate center, an outcome that could have been foreseen by x-ray studies.)*

J. B. (No. 117408), a woman, had a right nephrolithotomy in 1938 at the age of 25; the stone was found to contain a large amount of phosphate and a moderate amount of oxalate. The serum calcium was high (12.1 mg. per 100 cc.), the serum phosphorus was low (2.7 mg. per 100 cc.), and a diagnosis of hyperparathyroidism was made. A parathyroid tumor was removed by Dr. Oliver Cope. There remained a small stone in the right kidney at the time of the parathyroid operation; this continued constant in size for the next 3 years. In June, 1941, however,

the patient was cystoscoped in an outside hospital and developed an infection with *P. vulgaris*. Thereafter the stone grew rapidly.

Although the center of the stone in x-ray films looked suspiciously like that of an oxalate stone, it was decided to attempt dissolution through a ureteral catheter. A No. 5 whistle-top catheter was introduced into the right kidney during her second pregnancy, she developed pyelitis. One year before admission she received a left nephrectomy because of calculus pyonephrosis. Six months later she had right renal colic and passed a stone. *None of the stones had been analyzed.* Four weeks prior to admission she developed complete anuria of 48 hours' duration and attempts at ureteral catheterization were unsuccessful.

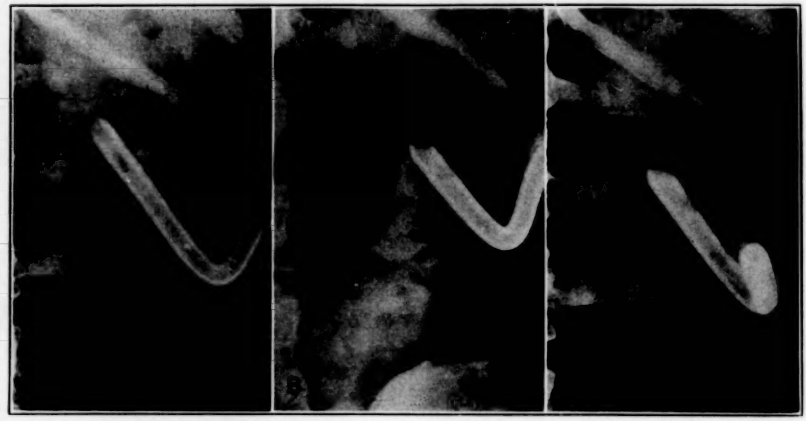

FIGURE 6. *Roentgenograms in Case 3 before* (A), *during* (B) *and after* (C) *Dissolution. Note that the stone is in contact with the pelvis, as shown in* B, *an air pyelogram.*

pelvis and left in for 24 hours, during 14 of which 5 cc. of Solution G was introduced every 5 minutes. This catheter did not work very well, however, and the patient complained of pain; accordingly it was withdrawn and a No. 10 Garceau catheter was passed. Five cc. of Solution G was injected into this catheter every 5 minutes for approximately 14 hours a day for 3 days. The Garceau catheter was then withdrawn and a No. 10 soft-rubber catheter was introduced. The irrigation was continued for 6 more days. Figure 7*A* shows the stone before irrigation, and Figure 7*B* after approximately 10 days of irrigation. It will be noted that the cortex of the stone was entirely dissolved. By more careful x-ray technic it was then demonstrated that the residual stone was calcium oxalate (Fig. 7*D*).

This case illustrates the importance of careful x-ray technic in order to rule out oxalate stones; had it been known, as it could have been, that the center of the stone was definitely oxalate, the procedure would have not been attempted. As a matter of fact, the patient's symptoms were very much improved as a result of the procedure, and it is barely possible that the size of the stone was sufficiently reduced so that it may eventually be passed.

CASE 5. *(Left kidney removed for calculus pyonephrosis; remaining kidney totally blocked by right renal stone requiring emergency nephrostomy; stones completely dissolved with Solution G; bladder irritability overcome by closed urethral drainage.)*

C. W. (No. 339467), a 25-year-old woman, was perfectly well until 1½ years prior to admission. At that time, A right nephrostomy was performed. The patient recovered from the operation and came under our control 3 weeks postoperatively. The wound was well healed, the nephrostomy tube was draining well, and she was passing nothing from the bladder. The blood calcium and phosphorus were within normal limits. The urine was alkaline and contained large amounts of pus; culture showed *Staphylococcus aureus* and a nonhemolytic streptococcus. An air pyelogram revealed a stone 2 cm. in diameter in the right ureteropelvic junction and several small stones in the lower calyx (Fig. 8*A*). These had the characteristic x-ray appearance of calcium phosphate stones. An attempt was made to ascertain the patency of the ureter at this time, but it was quite difficult to get liquid or air into the kidney pelvis. As salt solution was dripped into the nephrostomy tube it leaked out around the tubing. The lower calyx and infundibulum were apparently partially blocked by stone and mucus. By means of the Murphy drip apparatus we were finally able to run in Solution G very slowly. It was as if an exit for the fluid had to be dissolved out first. However, the lower calyx stone dissolved and the large pelvic stone began to crumple (Fig. 8*B*); later the larger stone completely disappeared (Fig. 8*C*). The patient had considerable bladder irritability once the solution began going through to the bladder. This complication was managed very easily by placing her on closed urethral drainage. Once she began to tolerate about 2000 cc. of fluid per day, the stone dissolved in about 10 days. Figure 8*C* is an air pyelogram showing that all the stones were dissolved. Figure 8*D* is a Neoskiodan pyelogram showing that, although there

was still moderate hydronephrosis, the ureteropelvic junction and ureter became patent. The right nephrostomy tube was removed, and the patient began to pass clear urine.

FIGURE 7. *Roentgenograms in Case 4.*

A — air pyelogram before dissolution; note the granular center and the less dense cortex of stone. B — stone after ten days of dissolution; note that the cortex has disappeared and that the remainder of stone has a granular appearance suggesting that it is an oxalate stone. C — larger magnification of A. D — a second roentgenogram of stone at same stage as B, with better x-ray technic to bring out the oxalate structure.

CASE 6. *(A 15-year history of kidney stones, including right nephrotomy; a diagnosis of hyperparathyroidism made, and a parathyroid adenoma removed; bilateral staghorn stones and pyelonephritis persisted; dissolution of stone on left through ureteral catheter.)*

E. R. (No. 135241), a 49-year-old, married woman, first developed urinary symptoms at the age of 30. Three years later the late Dr. Arthur Chute removed three "alkaline stones" from the right kidney pelvis. Eleven years later she was referred to the clinic by Dr. Harvard H. Crabtree because of bilateral staghorn kidney stones. Since there were hypercalcemia (serum calcium, 12.8 mg. per 100 cc.) and hypophosphatemia (serum inorganic phosphorus, 2.3 mg. per 100 cc.), a diagnosis of hyperparathyroidism was made. A parathyroid adenoma was removed by Dr. Oliver Cope in June, 1938. (This patient was one of the two in the series of 68 patients with proved hyperparathyroidism who did not have an abnormally high calcium excretion in the urine when first seen.) She had an infection in the urine with the urea-splitting organism, *Staph. albus*, and was unable to acidify her urine. The phenolsulfonephthalein excretion was excellent, but the urine concentration failed to rise above a specific gravity of 1.012.

After the removal of the parathyroid adenoma the serum calcium and phosphorus values returned to normal, but otherwise there was no change in the patient's condition.

To be sure, the urinary calcium excretion fell from a normal level (about 90 mg. in 24 hours) to a low level (about 35 mg. in 24 hours). During the next 5 years she was followed in the Out Patient Department. The staghorn stones remained constant in size; the kidney function remained relatively unaltered. Small calculi were passed from time to time; these presumably were new stones due to the persistently alkaline urine.

On April 21, 1942, an inlying soft-rubber catheter was introduced into the right kidney pelvis and dissolution of the stone with Solution G was started. The apparatus employed is shown in Figure 2. Two nurses were obtained, one for each of two 8-hour shifts; it was their duty to introduce Solution G by a syringe into the catheter every 4 to 10 minutes, to allow the solution to remain in the kidney 2 or 3 minutes, and finally to let it drain from the kidneys. As the stones dissolved away it was possible of course to introduce more fluid at a time; the largest amount used was 30 cc. The results are shown in Figure 9.

CASE 7. *(Bilateral calcium phosphate and carbonate stones; etiology probably excessive intake of soda and cheese; left nephrectomy and right nephrotomy performed previously; attempt to dissolve stone in right kidney through ureteral catheter; cause of failure shown by x-ray study.)*

R. W. (No. 354198), a 47-year-old, married woman, was admitted because of right renal stone. A left nephrectomy and right nephrotomy had been performed 1 year previously. The patient was for a long time in the habit of ingesting large amounts of soda and cheese. Stones removed at two previous operations contained large amounts of calcium phosphate and calcium carbonate.

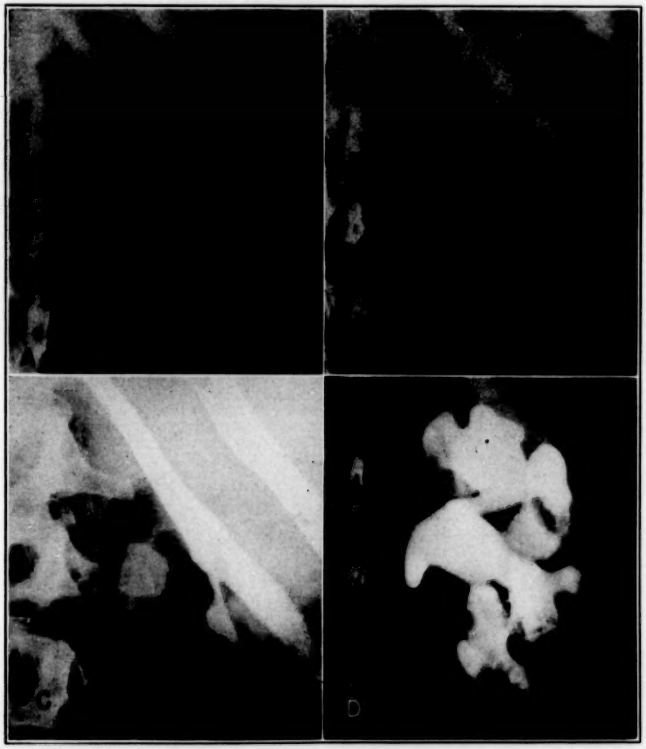

FIGURE 8. *Roentgenograms in Case 5.*

A — air pyelogram showing stones before dissolution. B — air pyelogram showing stone in lower calyx completely dissolved. C — air pyelogram showing all stones dissolved. D — pyelogram with opaque substance to compare with air pyelogram C.

FIGURE 9. *Roentgenograms in Case 6.*

A—before irrigation; B, C and D—eleven, twenty and forty days, respectively, after onset of irrigation. Note that dissolution proceeded most rapidly in the calices. This was an unexpected result since it was feared that calyx stones would be the last to disappear.

The last stone removed from the right kidney was noted in addition as having a peculiar coating, the exact nature of which was not determined but which was thought to be clotted blood since it gave a strongly positive guaiac test. The serum calcium and phosphorus levels were within normal limits. A ureteral catheter was introduced into the right kidney pelvis and irrigations were carried out as in Case 5. Re-examination 6 days later showed no decrease in the size of the stone. Failure was undoubtedly due to the capsule of organic material surrounding the stone, which prevented its solution (Fig. 10*A* and *B*).

FIGURE 10. *Roentgenograms in Case 7.*

A—stone before attempted dissolution. B—pyelogram with opaque substance after failure to dissolve the stone. Note that the stone is coated with some substance that prevents the opaque material from coming in contact with it.

SUMMARY AND CONCLUSIONS

Citrate solutions, rendered less irritable by the addition of magnesium, are practical for the dissolution of urinary calculi composed of calcium phosphate, calcium carbonate or magnesium ammonium phosphate.*

Six selected cases are reported in which such a solution was used successfully for the partial or complete dissolution of stones; in 2 cases the solution was introduced through ureteral catheters, in the remaining 4 through nephrostomy tubes.

One case is reported in which attempted dissolution of a large stone was without success because the solution was prevented from coming in contact with the stone by a thin coating of unidentified material, possibly old blood clot.

The choice of apparatus depends on the individual case and the ingenuity of the operator. Ideally the hydrodynamics should be such that the pressure in the kidney is great enough to get the solution around the stone, but sufficiently intermittent so that a pyelonephritis is not produced by a constant back pressure.

For determining whether a stone is in contact with the kidney pelvis and for following the course of dissolution, the advantages of an air pyelogram are stressed.

The importance of the roentgenogram in determining whether the stone is of the soluble variety is pointed out; a case is cited in which the centre of the stone was calcium oxalate and hence indissoluble, a finding that could have been determined by suitable x-ray technic.

*The slight irritability of Solution G is probably caused by the fact that its pH is lower than that which the urine reaches. It may be that a solution with a pH of 4.5 would in the long run be better. What one would lose by the decreased speed of solution one might gain by the lack of irritability.

The formula for such a solution (Solution M) is as follows:

Citric acid		32.35 gm.
Sodium carbonate (anhydrous)		8.84 gm.
Magnesium oxide		3.84 gm.
Water	q. s. ad	1000 cc.

As judged by its ability to dissolve rabbits' teeth, Solution M will do in twelve hours what Solution G will do in eight hours.

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EPIDEMIOLOGIC ASPECTS OF ANTHRAX IN MASSACHUSETTS*

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BOSTON

TIMES of war bring a host of new problems and an intensification of old ones in medicine as well as in many other fields. Anthrax, known since antiquity as an agricultural disease, presents in these days of stress an increased potential industrial hazard, for, in the anxiety to get leather, hides are obtained wherever available. Many are imported from countries where anthrax is still a common disease. In this connection it may be mentioned that in 1938 in Bulgaria, with a population of only 6,500,000, between 800 and 1000 human cases and 2716 animal cases of anthrax occurred.[1] At present, many hides in the United States come from India and China, countries where anthrax is prevalent.

With the wartime influx of potentially infected hides, the epidemiologic control of anthrax presents a greater problem than ever. Public-health supervision of importation and transportation is imperative. Smyth,[2] in a twenty-year survey in the United States (1919–1938), reported an incidence of 1683 cases. In Massachusetts, in the seven and a half years, from January, 1935 to July, 1942, 43 cases have been reported. That the incidence has not been greater is merely fortuitous, and it may rise rapidly in the near future. Anthrax spores are extremely difficult to kill; and to this day no commercially practicable method of destroying spores in hides has been discovered, since all known methods are complicated and expensive. Although this was the first disease entity to be proved by Koch's postulates,[3] no significant advances in its control have been made in the last twenty years.

Man and all animals, especially the herbivora, are susceptible to infection with *Bacillus anthracis*.[4] Normally the organism is indigenous only in certain areas, called "anthrax districts," and in such places animals are sporadically infected during some period of the year, usually in the summer. Isolated cases, however, may occur at any time. Anthrax being primarily a disease of animals, it frequently happens that agricultural workers become infected. It is also apparent that workers who deal with any by-product of an animal may contract the disease; included among such workers are those who deal with hides, wool, bristles, and hair. Longshoremen, truckmen and a group of miscellaneous workers, such as brushmakers, butchers, gluemakers and upholsterers, may also be infected. In animals, anthrax is caused by ingestion and any medium that spreads the bacillus may cause an outbreak. In man the spore usually enters through a break in the skin, forming the so-called "malignant pustule." It may, however, be ingested and, in some cases, as in woolworkers, may be inhaled, giving rise to the pulmonary form of the disease.

In 1940, the United States Bureau of Animal Industry[5] decided that the possibility of the spread of anthrax to domestic animals from imported fomites was relatively slight and, with certain specified exceptions, lifted its restrictions on the importing of hides. It is important to recognize that this bureau is interested primarily in the control of animal disease and not in the control of human disease. Theoretically, consular inspection at the point of origin of foreign hides is maintained. In normal times this inspection is subject to error, and under the stress of war it can at best be only perfunctory. Dry hides that are imported are subject only to a treatment (with bifluoride or silicofluoride) known to be effective against rinderpest and hoof-and-mouth disease. The effect of this treatment on anthrax spores is unknown and may be presumed to be nonefficacious, since infections have occurred from hides that have been treated in this manner.[6]

There have been 4 deaths and 39 recoveries in the 43 cases that occurred in Massachusetts from 1935 to 1942. The incidence by years is shown in Table 1. An average of 5.7 cases a year have occurred. The lowest incidence was in 1939, with only 2 cases, which was followed by a sharp increase to 9 in 1940. In 1941 there was a decline to 6 cases, and in 1942 up to the present writing (July 1), 3 cases have been reported.

TABLE 1. *Anthrax Morbidity and Mortality.*

YEAR	NO. OF CASES	NO. OF DEATHS	MORTALITY %
1935	3	0	0
1936	9	1	11
1937	6	0	0
1938	5	1	20
1939	2	0	0
1940	9	0	0
1941	6	1	16
1942 (to July 1)	3	1	33
Totals	43	4	9.3

The occupations involved are shown in Table 2. Massachusetts has a large leather industry, and this is reflected in the fact that tannery workers

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†Physician, Division of Occupational Hygiene.

account for 32 cases comprising almost three quarters of the total. The majority of men infected worked either in beam houses or in storehouses.

TABLE 2. *Incidence of Anthrax according to Occupation.*

OCCUPATION	NO. OF CASES	NO. OF DEATHS	MORTALITY %
Tannery workers	32	1	3
Truckmen and longshoremen	4	2	50
Hair and bristle workers	3	1	33
Agricultural workers	2	0	0
Woolsorter	1	0	0
Miscellaneous (welder)	1	0	0

No authentic case could be traced to infection from finished leather. The next largest group, truckmen and longshoremen (4 cases), were all engaged in the transportation of imported hides. One more case could be traced to hides, as a welder was infected from his equipment, which had become contaminated by unfinished leather. Hence, in all, a total of 37 out of 43 cases, or 87 per cent, occurred in connection with hides. In not a single case could the infection be definitely traced to domestic skins. In 1 case it was thought to be due to domestic sheepskins, but the tannery concerned handled large amounts of imported hides, and the chance of cross-infection was considerable. In an overwhelming majority of cases goatskins coming from India or China were the responsible agents. Four tanneries account for the major amount of imports, and in them occurred 27 cases or 63 per cent.

Three cases occurred among workers in hair and bristles, one of whom developed the only case of internal anthrax in this series. This man had both cutaneous and intestinal lesions and died. Certain by-products of animals, especially hair and bristles, are still subject to sterilization; hence, although outbreaks do occur, they are relatively rare. Two cases occurred in men engaged in domestic agricultural pursuits. One was a veterinarian who autopsied the carcasses of several cattle that had died of anthrax; the other was the owner of a mink farm where the animals became infected by eating anthrax-infected horsemeat. One case occurred in a woolsorter who scratched himself and developed cutaneous anthrax.

Although only 4 truckmen and longshoremen were infected with anthrax, 2 of them died. This high mortality, although not significant because of the small number of cases, is directly attributable to the lack of knowledge of the hazard of the disease on the part of the transportation companies and their employees. It was, therefore, not recognized until late, with a consequent delay in therapy. Among tannery workers, where anthrax is suspected in any cutaneous infection, diagnosis and treatment are prompt, with a consequent decrease in morbidity and mortality. In the 32 cases that occurred in this group, there was only 1 fatality.[7]

SUMMARY AND CONCLUSIONS

It appears to be impossible to destroy anthrax at its source. Sporadic cases of native origin will always occur. It is extremely difficult to disinfect hides and skins. The anthrax spore undoubtedly survives the first two or three processes in tanning — that is, washing, fleshing and liming — but probably cannot survive the entire process. No significant improvement in the method of killing anthrax spores has been evolved in the last twenty years; and even if it were possible to disinfect hides and skins, it is doubtful whether this would be warranted, especially at the present time. Therefore the method of control must be chiefly one of education and sanitary precaution until the hides have passed through the tanning process. The more severe cases and the most frequent deaths have occurred in truckmen and longshoremen, who are not aware of the possibilities of this infection and who neglect to report for treatment early. The prompt diagnosis and treatment in tannery workers seem in large measure responsible for the lessened mortality and morbidity among them. Physicians treating any cutaneous infection in a tannery worker or truckman should bear in mind the possibility of anthrax and should culture material from the lesion. In order to keep this disease in check effectively, an educational program must be directed toward truckmen, tannery workers, longshoremen and all others who handle imported hides, from their arrival in this country to their conversion into finished leather.

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MONTESQUIEU: A BIOLOGIST OF THE EIGHTEENTH CENTURY

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IN HIS profound study of the development of modern medicine, Shryock,[1] speaking of the physicians of the eighteenth century, points out that Voltaire, the great lay critic, held saner views on medicine than did most of his professional compatriots. This fact constitutes perhaps one of the most striking features of the beginning of this remarkable century. The men who were guided by reason only, the "philosophers," did not have to overcome the bookish prejudices that surrounded stagnant medicine like a Chinese wall. For although at this time medicine was greatly harmed by Molière's biting mockery, it continued nonetheless to be merely a study and an interpretation of classical texts — as one might say, *more theologico*.

Medicine progressed with slower steps than did the other sciences. Where, indeed, are the physicians of this period who can be ranked with Linné, Buffon, Volta and Galvani?

Along with Voltaire, Shryock should have been able to quote Charles Louis de Secondat, Baron de la Brède et de Montesquieu (1689–1755), who throughout his work never ceased taking a great interest in medicine and physicians. The author of *L'Esprit des lois*[2] and *Lettres persanes*[3] merits a place in medical history. I am sorry to state that I could find no mention of him in classical treatises.

I shall aim to fill the gap concerning a man who is considered rightly as one of the most humane and most eminent writers of French literature and whom physicians can be proud to count as one of theirs.

How did this man treat the field of medicine?

The Academy of Bordeaux, of which Montesquieu had been a member since 1716, had chosen as the prize subject "The function of the renal glands or atrabiliary capsules" (we should say, "The physiology of the suprarenal glands"). On August 25, 1718, Montesquieu announced in a speech before this esteemed society that the prize of the Academy could not be awarded to any competitor. In a clear statement, which showed his deep knowledge, he gave the reasons for this decision. But his interest was attracted by an abstract that had been submitted.

> Another [he said] who fortunately defined the difference between conglobated and conglomerated glands considered the atrabiliary capsules as a conglobated one. He believes that they are only a continuity of vessels in which the blood like in channels is subtilized. . . . In these glands, and in every conglobated gland, there is no excretory duct, because there is no matter to separate liquids, but only to subtilize them. This system, not without some appearance of truth which is captivating at first, had attracted the attention of the society. But the author could not maintain his thesis.

And while the author of this luminous hypothesis still remains unknown, Montesquieu at least deserves credit for having transmitted it to our admiration. We know today how true this thesis was! But it was a long time before our knowledge was acquired. Anatomists like Gegenbaur† rejected even in 1903, about two centuries after the meeting of the Academy of Bordeaux, the idea of glands in which the excretory duct is supplied by blood vessels. Can we, therefore, upbraid Montesquieu for having doubts about this thesis, which seemed unlikely even to unquestionable masters of anatomy in our time? The members of the Academy assured themselves of the difficulties of the subject. They ordered experiments and dissections to be made so that they could "see with their own eyes," and thus they understood why the solution of the thesis had not been found.

"Chance will perhaps do some day," Montesquieu added, "what every effort could not do." And he closed his speech with these words which investigators can use as a motto:

> Those who make their profession the seeking of truth are no less subject to the caprice of fortune than are others. What today costs so much needless toil can perhaps not withstand the first considerations of a happier author. Archimedes found while taking a delightful bath the solution of the famous problem which he had missed a thousand times while reflecting deeply. Truth seems sometimes to run before the seeker. Frequently there is no interval between desire, hope and enjoyment. Poets tell us that Pallas went out of Jupiter's head without pain, to make us conscious that the products of the spirit are not always tiresome.

The "Observations on Biology," which Montesquieu read on November 20, 1721, merits our admiration because it demonstrates the probity and the scientific spirit of the author. What a diversity of related facts! The pigmentation of insects was studied microscopically, the parasitism of mistletoe was examined carefully, the abdominal circulation

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†Gegenbaur[4] writes: "We used to range thyroid and thymus along with some other glands, which have a 'mysterious' physiology, as 'blood glands.' Some authors consider them as glandular organs in which the excretory duct is replaced by blood vessels. The excretory duct, however, constitutes an essential part of a gland, which cannot be supplied by blood vessels. It is by no means evident how blood vessels physiologically can supply a part of an organ or how these organs secrete something that goes into the blood."

of the frog was exposed with great precision. Finally, many problems of vegetal physiology, as well as studies on the foramen ovale and Botallo's duct, are noteworthy. The last chapter of these observations concerns experimental researches on the nutritional value of some vegetables.

> One imagines [he wrote] that only wheat has food value for the human being and one considers that the other plants are merely of medical use. Physicians find them emollient, diuretic, desiccative or astringent. They treat all like manna, which nourished the Jews, and which they use as a purgative. They give them an infinity of qualities which they do not have and nobody thinks of the nutritional virtue which they have. Wheat, barley, rye, like other plants, have years which are very favorable to them. There are years when the scarcity of corn does not constitute the unique misery which causes sorrow to people. Their bad quality is still more cruel. In these years, calamitous for the poor and a thousand times more calamitous for the rich, in a religious nation, we are able to supply the deficiency of corn. We have under our feet in every wood a thousand resources against dearth, and for that we should praise instead of curse Providence if we would know all his benefits. And therefore we intend to examine plants, barks and an infinite number of things which apparently have no nutritional virtues. Animals which have some resemblance to human beings can well be used for this purpose. We have begun some of these experiments with great success. The shortness of time does not permit us to quote them here.

What a pity that this report did not come down to posterity! Montesquieu told us that his research work was the fruit of leisure hours in the country. For the author of *L'Esprit des lois* considered that leisure must be profitable to mankind. "Those who are living in a community," he wrote, "have to fulfill a duty; we have to account for every diversion."

Thus the lucid Montesquieu could only condemn and distrust the medicine of his time. He thought that the human spirit was stifled in the heap of theses of an obsolete and absurd "science." He held in abhorrence "this dreadful army of glossators and compilers who are as weak through the dullness of their advice as they are strong through their tremendous numbers." "And that is not all," he continued; "these foreign [Roman] laws have introduced formalities so excessive as to be a disgrace to human reason." And, again, "It would be very difficult to decide whether the pedantry has been more harmful in jurisprudence or in medicine, whether it has played more mischief under the cloak of a lawyer or the broad brim of a physician, and whether the one has ruined more people than the other has killed."

In a letter from a country physician to a physician of Paris, the mockery of Montesquieu reaches a peak:

> There was once in our town a sick person who had no sleep for thirty-five days. His physician ordered him opium; but he could not make up his mind to take it, and when he had the cup in his hand he was less inclined than ever. At last he said to his physician: "Sir, give me only till tomorrow: I know a man, who, although he does not practice medicine, has in his house an immense number of cures for insomnia. Let me send for him, and if I do not sleep tonight, I promise to return to you." The physician being dismissed, the sick man had his curtains closed, and said to his page, "Go to M. Anis and ask him to come to me." When M. Anis came, the patient said to him: "My dear sir, I am dying; I can't sleep. Have you not in your shop the *Connaissance du globe* or some other book of devotion written by an R. P. I. which you have not been able to sell, for long-kept remedies are often the best?" "Sir," replied the bookseller, "I have the *Holy Court* of Father Caussin, in six volumes, at your service. I will send it to you, and I hope you will be the better for it. If you would prefer the works of the Reverend Father Rodrigo, a Spanish Jesuit, you need not want them. But believe me, you had better stick to Father Caussin. I trust, with the help of God, that a single sentence of Father Caussin's will do you more good than a whole page of the *Connaissance du globe*." With that M. Anis left and went to his shop to get the remedy. The *Holy Court* arrived, and the dust having been shaken off of it, the son of the sick man, a schoolboy, began to read it. He was the first to feel its effects. At the second page his utterance began to be almost inarticulate, and already the whole company was growing drowsy. In a moment everybody was snoring except the sick man, who, after having stood it a good while, was at last overcome too.
>
> The physician arrived early next morning. "Well," he said, "has my opiate been taken?" Nobody answered him. The sick man's wife, daughter and little boy, radiant with joy, showed him Father Caussin. He asked what it was. They answered: "Long life to Father Caussin; we must send him to be bound. Who would have said it, who would have thought it? It is a miracle. Look, sir, look, here is Father Caussin. It is this book which has given my father sleep." And thereupon they explained the matter to him as it happened.
>
> The physician was a skillful man, versed in the mysteries of the Cabala, and in the power of words and spirits. He was much struck, and, after deep thought, resolved to change his practice entirely. "Here is indeed a notable fact," said he. "It is a new experience, and I must experiment further. And why should a spirit not be able to transmit to its work the same qualities which itself possesses? Do we not see it every day? At least it is well worth the trying. I am tired of the apothecaries, their syrups, the juleps, and all their galenical drugs destroy the health and the lives of their patients. Let us change the methods, and try the power of the spirits." With this idea, he drafted a new system of pharmacy, as you will see by the description which I am about to give you of the principal remedies which he employed.
>
> A Light Purgative
>
> Take three leaves of Aristotle's *Logic* in Greek; two leaves of a treatise on scholastic theology, the keener the better, as, for example, that of the subtle Scotus; four of Paracelsus; one of Avicenna; six of Averroes;

three of Porphyry; as many of Plotinus; and as many of Iamblichus. Infuse the whole for twenty-four hours, and take four doses a day.

This is only one example of a long list of prescriptions of the same kind. It would be too tedious to quote them. His favorite authors, I suppose, are not used as an ingredient of any decoction, even as an emollient one!

• • •

"We have enough physicians. We now need medicine," he exclaimed once. He knew that there was no parallelism between medicine and the other sciences concerning progress.

> Books of medicine [he wrote to express the same idea], those monuments of the frailty of nature and of the power of art, which, when they treat even of the slightest disorders, make us tremble by bringing the idea of death home to us; but which, when they discuss the power of remedies, make us feel as secure as if we were immortal.
>
> Near these are the books of anatomy which do not so much contain descriptions of the parts of the human body as the barbarous names which have been given them — neither likely to cure the patient of his disease nor the physician of his ignorance.

People would perhaps blame Montesquieu for entertaining prejudices concerning medicine and physicians. Some may believe that his critical spirit prompted him to laugh at everybody and everything. But, satirizing with brilliant audacity the follies of his time, he could not avoid taunting our profession.

In a letter written May 5, 1753, to his good friend, Father de Guasco,* he expressed great admiration for Van Swieten, who was called by Maria Theresa from the Netherlands to Vienna to reorganize medical education. This famous physician, who was also chairman of the board of censors of Austria, authorized that Montesquieu's book *L'Esprit des lois* could be sold in the Austrian Empire. Montesquieu held in devoted affection his physician Chevalier Louis de Jaucourt, who was a collaborator in the *Encyclopedia* for the section of physiology and pathology.

*Who was also a friend of Lord Chesterfield

Montesquieu, who with his brilliant intelligence inquired into charges against the institutions and customs of his time, had to speak in his list of accusations of medicine and physicians. In the Academy he showed which way medicine had to take if the physicians would avoid irreverence and ridicule.

Antoine Portal, professor of anatomy of the Collège de France and the Jardin du Roy, gave this praise of Montesquieu: "We cannot say without admiration that, if Montesquieu had applied himself to anatomy, the progress of this science would have been as important as that of the ethical sciences under his guidance."

The mockery of *Persian Letters* is worthy of Molière's plays. Montesquieu's probity would not have permitted an unjust attack. He was a sincere moralist. "I never saw weeping without being moved with pity. I have committed many blunders during my life but never a malicious act."

He once wrote this sentence, which should win him immortality: "If I should know something useful to my fatherland but detrimental to Europe and mankind, I should consider it a crime." But Montesquieu knew that by remaining passionately a Frenchman he could be a good citizen of the earth.

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MEDICAL PROGRESS

OBSTETRICS: MEDICAL ASPECTS

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AMONG the medical aspects of obstetrics, the toxemias of pregnancy continue to hold the center of interest because of their general influence on the occurrence of hypertension and albuminuria in women. Various attitudes regarding the relation of these conditions in pregnancy to the general problems of vascular and renal disease have led, in the past, to many differences of opinion. Contradictory results were often found, not only in clinical studies of these diseases but also in the physiologic studies made on patients. To promote a better understanding of the clinical syndrome known as the toxemias of pregnancy, a universal classification of diagnosis appeared most desirable. Through the American Committee on Maternal Welfare such a classification was presented in 1940[1]; it has been accepted, and is now being used by all the large obstetric clinics of this country. This has been a landmark in the advance of the study of this disease for, although the classification may have certain weaknesses, it offers an opportunity to provide an accurate diagnosis in terms that are familiar to all. To emphasize the importance of this classification, it is given below.

GROUP A. Diseases not peculiar to pregnancy.

1. Hypertensive disease (hypertensive cardiovascular disease).
   - *a.* Benign (essential).
   - *b.* Malignant.
2. Renal disease.
   - *a.* Chronic vascular nephritis or nephrosclerosis.
   - *b.* Glomerulonephritis.
   - *c.* Nephrosis.
   - *d.* Other renal disease (such as pyelonephritis).

GROUP B. Disease dependent on, or peculiar to, pregnancy.

1. Pre-eclampsia.
   - *a.* Mild.
   - *b.* Severe.
2. Eclampsia.
   - *a.* Convulsive.
   - *b.* Nonconvulsive (that is, with coma and post-mortem findings typical of eclampsia).

It is evident from this classification that the obstetrician is aware of the role that vascular disease and renal disease play as a background for the toxemias of pregnancy (Group A). He also knows that the majority of patients with this syndrome develop, for the first time during pregnancy, varying degrees of albuminuria and hypertension (Group B). Finally, it is also realized that occasional cases may require a combined diagnosis from Group A and Group B, that is, pre-eclampsia superimposed on pre-existing vascular or renal disease.

With such a classification in universal use, and with the pooling of the experience from many clinics, it is possible to offer a solution of some of the problems that are bothersome during pregnancy, as well as to evaluate the renal and vascular sequelae that follow a toxemic pregnancy. Some of the more pertinent medical questions might be the following:

Which individuals with established vascular or renal disease should be allowed to continue their pregnancies?

If such patients are allowed to continue their pregnancies, what is the maternal and fetal risk involved?

What would be the effect of pregnancy on the course of the previously established vascular or renal disease of the mother?

What are the sequelae of the so-called "specific toxemia of pregnancy" on the vascular or renal system of previous normal persons?

Although many observations have been made to determine the ante-partum and post-partum status of the vascular and renal systems of patients in the different groups, no uniform answers to these questions have been given by the clinicians.

Albuminuria being a constant finding in the toxemias of pregnancy, attention was first focused on the kidney as the organ most profoundly affected by the course of this disease. However, it was soon found that marked changes could be observed in the liver, brain and other vital organs. Moreover, the degree of these changes was extremely variable. It has been emphasized that they are best explained by damage to the vascular system, particularly the small arterioles. Spasm of the smaller vessels oc-

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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curs with marked capillary damage; this in turn, results in multiple hemorrhages throughout the body.

To ascertain possible alterations in blood flow to the kidney during a toxemic pregnancy, Taylor and his co-workers[2] have studied a small series of patients with specific (Group B) toxemias. In addition, studies were carried out on a somewhat larger series of patients whose blood pressures and urines were normal during the course of their pregnancies.

Diodrast- and inulin-clearance studies were done in both groups. In brief, these procedures reveal information regarding the filtration rate of the glomerulus and the excretory function of the tubules, as well as the effective blood flow through the kidney. The blood supply to the individual nephron of the kidney is a small division of the renal artery. The small afferent arteriole enters the glomerulus and forms the capillary loops within Bowman's capsule. It then emerges from the glomerulus as the efferent arteriole, to redivide itself into a secondary capillary network to supply blood to the complete unit of the tubule associated with the glomerulus. Inulin is a polysaccharide of high molecular weight that is filtered by the glomerulus (filtration rate), and is not reabsorbed or excreted by the tubules. Diodrast is excreted only by the tubules. Because the latter material passes through the glomerular capillary loops and on to the tubules, not only is the amount of Diodrast excreted evidence of tubular function, but if the hematocrit is known, the plasma-Diodrast clearance can be transferred into terms of actual renal blood flow.

Taylor and his co-workers have shown that the filtration rate, tubular function and renal blood flow were unaltered in 20 pregnant women whose courses during pregnancy were normal. In 13 pregnant women whose blood pressures and urines were normal through the second trimester of pregnancy but who developed specific toxemias (Group B), the following was revealed; first, there was a slightly reduced filtration rate ante partum, returning to normal following delivery; the filtration rate became high in 6 patients who subsequently developed post-partum hypertension; and secondly, the renal blood flow was unaltered ante partum, but became reduced in those patients who developed persistent post-partum hypertension. It is apparent that *renal ischemia is not the cause of the hypertension of the toxemias of pregnancy, unless there is some unknown protective substance present only during pregnancy.* Furthermore, it would appear that, as hypertension develops post partum (6 out of 13 cases), the decreased blood flow and rising filtration rate are consistent with benign hypertension in the nonpregnant. These observations, if substantiated, appear extremely important and fundamental.

However, one must be critical of the correlation of the clinical picture of these patients and the laboratory findings. The picture is not clear concerning the amount of hypertension, albuminuria and edema present. As there was no evidence of decreased urinary output — that is, inulin values were normal — it might be supposed that the cases were mild in character. If this is true, the findings are less significant since many observers have noted that the incidence of post-partum hypertension is higher in mild cases than in severe. It has been postulated that this is due to the fact that these patients are predestined to become hypertensive, irrespective of pregnancy toxemia and that the load of pregnancy is a test of vascular integrity. However, Taylor and his co-workers have supplied direct evidence that a definite stigma was left on the vascular bed of the kidneys in nearly half the patients studied. Further studies on the more severe preconvulsive-convulsive groups are awaited with interest.

The effects of the alkaloids of veratrum viride have been reviewed previously in this journal[3, 4] because of the good results reported in the treatment of eclampsia.[5] The pharmacology of these substances has been little understood, owing in part to the fact that pure samples of each of them have not been obtained. It has long been known, however, that marked physiologic changes in the vascular system can be produced by these drugs. Except for the fact that they produce strong vagal action, little is known regarding their action on the peripheral blood vessels or the heart muscle itself.

The clinical use of these alkaloids in the treatment of hypertension, particularly that associated with eclampsia, has been accompanied by a renewed interest of the pharmacologists. Krayer and Mendez,[6] using a mixture composed for the most part of the alkaloid veratrine (a component of veratrum viride), have studied its action on the heart-lung preparation of the dog. These investigators found that there is a direct action of the drug on the heart muscle, with some slowing of the heart rate and slightly increased coronary blood flow. This action is more marked if the heart is failing. The heart muscle does not react with the same activity, however, if the drug is repeated for several doses.

What is not known regarding the action of this drug is the effect on the arterioles. This would be important knowledge in gauging its therapeutic value in the treatment of eclampsia.

From a clinical point of view, considerable change is seen in the blood pressure and heart rate of patients with hypertension associated with

pre-eclampsia and eclampsia when treated with veratrum viride. At the Boston Lying-in Hospital, in a series of 20 cases equally divided into cases of eclampsia and severe pre-eclampsia, the blood pressures and pulse rates were rather markedly reduced.[7] In the pre-eclamptic group, the average drop in systolic pressure was 92 mm., and in diastolic 56 mm.; and in the eclamptic group, the average drops were 94 and 55 mm. respectively. The average drops in pulse rate in the two groups were 24 and 40 beats per minute, respectively.

Continued interest and added data have accumulated regarding the influence of the Rh factor in intragroup blood-transfusion reactions,[8–11] and its relation to erythroblastosis foetalis.[12] The agglutinogen has been shown to occur in the bloods of 86 per cent of all human beings,[8, 9] and is a Mendelian-dominant factor. Therefore, if an Rh+ father is mated with an Rh− mother, the fetus will exhibit the Rh+ factor having inherited it from the father, and the Rh+ fetal blood may gain access to the maternal circulation, with resulting isoimmunization of the mother through the formation of anti-Rh agglutinins. These antibodies may then pass through the placenta and produce hemolysis of the fetal blood. The degree of blood destruction in the fetus depends on the titer of the anti-Rh agglutinins and the length of time the fetus is exposed to such antibodies.

It must be remembered that the mode of transference of these agglutinogens and anti-Rh agglutinins between the maternal and fetal circulations is not known. Javert[13] has recently described the presence of intraplacental hematomas in certain cases of erythroblastosis. He postulates that numerous monoblasts and erythroblasts are present in the areas where these agglutinogens and agglutinins are transmitted back and forth between the maternal and fetal circulations. However, Javert aptly says, "The inheritance of the Rh factor and its relationship to isoimmunization appear to be established, but conclusions as to their role in the etiology of erythroblastosis must be held in abeyance for the present."

Determination of the Rh factor in the parents and of the anti-Rh factor in the mother have been well enough established to make these tests of definite clinical use. Certain situations may be enumerated in which the test appears to be of value, as follows:

(1) Cases in which stillborn infants are encountered and in which the cause of death is not determined by direct tissue examination of the placenta or by necropsy.

(2) Cases in which the diagnosis of erythroblastosis foetalis has been made in a previous pregnancy and in which the mother presents herself for possible therapeutic abortion. The presence or absence of the anti-Rh factor may be a determining factor in arriving at a decision.

(3) Cases like the above in which it has been decided that the pregnancies should continue because of the absence or a low titer of anti-Rh agglutinin. Monthly determinations of the anti-Rh factor in the blood of the mother may be of clinical value. A rising titer in the last six weeks of pregnancy may justify its artificial termination in the hope that the cessation of blood destruction in the infant, effected by delivery, will outweigh the risk of prematurity. The disease then being relatively mild, an increased infant salvage may result if blood transfusions are given to these infants immediately after birth.

Many of the factors already considered are applicable to the proper conduct of blood transfusion. The Rh factor has been shown to be a definite hazard in intragroup transfusion reactions. This is particularly true in persons without the Rh factor (Rh−) who have had repeated transfusions. In obstetrics, one has in addition the Rh+ fetus, which may produce isoimmunization of the Rh− mother. Because of this it has been the practice of certain maternity clinics not to use the father as a donor. Ideally, perhaps, every obstetric patient should be properly typed and the Rh factor determined in the antenatal period. In many large medical centers the material for these tests is now available for use. Certainly, the blood from Rh− donors should be made available in every hospital for the transfusion of the occasional Rh− patient. However, this is not always feasible if the occasion is an emergency and the replacement of acute blood loss is imperative.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 29031

PRESENTATION OF CASE

A thirty-nine-year-old man came to the hospital because of recurrent fractures of the right humerus.

Twelve years before entry the patient first broke his right humerus, while engaging in an arm-wrestling game. At this time the arm was immobilized in a sling for six weeks. Six years later, while hammering with a 5-pound mallet, the fracture recurred. After six weeks of immobilization in a sling, union was apparently firm. One and a half years before admission the humerus was again fractured when the patient attempted to raise himself through a trap door. The treatment was similar to and as successful as that previously employed. Two days before entry, following what seemed to be slight trauma, the fracture recurred. The patient believed that though the same bone was involved each time, the fractures did not occur at the same level.

The family and past histories were noncontributory. He had never fractured any other bone.

Physical examination disclosed a well-developed and well-nourished man in no obvious distress. The examination of the lungs, heart and abdomen was negative. There apparently were false motion and soft-tissue swelling at the junction of the middle and lower thirds of the shaft of the right humerus, with slight anterior displacement of the distal fragment. The bones did not seem massive, and the skull was not enlarged. There was some pigmentation on the back.

The blood pressure was 112 systolic, 66 diastolic. The temperature was 97.6°F., the pulse 60, and the respirations 20.

Examination of the urine revealed a specific gravity of 1.018 and a neutral reaction; the sediment contained only a great deal of amorphous material. The blood Hinton test was negative. The blood calcium was 11.6 mg., the phosphorus 4.48 mg. and the phosphatase 17.1 Bodansky units per 100 cc.

An x-ray film demonstrated gross abnormalities of the right humerus in the upper three fourths (Fig. 1). There were large irregular areas of rarefaction along both the cortical and medullary portions, giving the bone a cystic appearance. There was expansion of the shaft in its middle third, whereas in the upper third the shaft was narrow and increased in density, with coarse tra-

FIGURE 1.

beculations. There was a pathologic fracture at the junction of the middle and lower thirds, with slight anterior displacement of the distal fragments. Several cyst-like areas were seen in the lower part of the bone and in the upper shaft of the radius. The uninvolved portions of the bone were not definitely decalcified.

On the third day after admission, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FULLER ALBRIGHT: I cannot remember ever getting one of these cases right. If I do not get this one right I will be surprised and chagrined.

I see very few problems here. "There was some pigmentation on the back." We should like to know what kind of pigmentation. No, we do not really want to know, because it is not that! By "that" I mean osteitis fibrosa disseminata, which is often accompanied by areas of café-au-lait pigmentation. But since pigmentation was mentioned, they might have told us what kind it was.

The phosphatase is high for an adult. Even for a fracture it is high.

This is really an x-ray problem, and all we have to do is look at the x-ray films and make a diagnosis.

DR. GEORGE W. HOLMES: All these films were taken on the same day. They show a cystic lesion that ends abruptly. There is normal bone in the lower half of the humerus, and pathologic bone above it. It is an extensive lesion, with marked increase in the trabeculation of the entire upper end of the bone. There may be slight periosteal proliferation. Do you attach any importance to the fact that it apparently involved the end of the bone?

DR. ALBRIGHT: No. It can do this in either osteitis fibrosa disseminata or in osteitis deformans (Paget's disease).

DR. HOLMES: In Paget's disease the lesion always goes to the end of the bone. I am not saying it is Paget's disease.

DR. ALBRIGHT: But I have seen at least one good case of Paget's disease that did not go to the end.

DR. HOLMES: That may have been the exception that proves the rule.

DR. JOSEPH AUB: Did you say this was Paget's disease, Dr. Albright?

DR. ALBRIGHT: No, but I am going to.

The pathologic process involves not only the humerus but also, according to the record, the radius on the same side. That makes us think of one disease in differential diagnosis, namely osteitis fibrosa disseminata. We do not have to think of any other. I should like to see x-ray films of the hand of the same side. If it were osteitis fibrosa disseminata, it is very likely that there would be cysts in the hands as well, since the cysts tend to run up and down one limb.

I do not believe there is any question about the diagnosis. Probably, I am away out on a limb, but I should not consider any other diagnosis than Paget's disease. The x-ray film is absolutely characteristic. There is a sharp line of demarcation between the abnormal and the normal bone. The phosphatase level fits in very well. I do not know of any lesion other than Paget's disease that would give so much elevation in phosphatase for such a small lesion. I presume he had no bone lesions elsewhere.

DR. TRACY B. MALLORY: None were discovered.

DR. ALBRIGHT: The question comes up, Why did he have Paget's disease? Can Paget's disease develop in a fracture? I have never known of a case where this has been proved to occur. One often gets the history of fracture and, later on, full-blown Paget's disease in the same region, but in such cases x-ray films have never been available in my experience to show that Paget's disease was there at the time of the fracture.

I do not believe we have to consider sarcoma. We always worry about it when the fractures of Paget's disease begin to occur. I see no evidence of it here. Furthermore, the phosphatase should have been higher. However, let me take another look at these films with the sarcoma idea in mind. Where was the fracture?

DR. HOLMES: I cannot see it in these films, which I agree with Dr. Albright are characteristic of Paget's disease.

DR. ALBRIGHT: That is all I have to say and it is probably too much.

DR. MALLORY: Are there any other expressions of opinion?

DR. AUB: I think one has to consider the possibility of localized bone cyst, with change in shape because of the two previous fractures. Is that possible?

DR. ALBRIGHT: The phosphatase is too high.

DR. AUB: Yes, but if he had a fracture, it might go up.

DR. ALBRIGHT: It will take a good microscopic section to tell which it is anyhow.

DR. MALLORY: What would you say about bone cyst, Dr. Holmes?

DR. HOLMES: One might consider it in view of the history of multiple fractures. There are certain things here to make one think of it. The explanation of the peculiar deformity I should attribute to fracture; it is very characteristic of Paget's disease. If it is not that, I do not know what it is.

DR. ALBRIGHT: The first fracture came too late in life for one due to bone cyst, which usually fractures earlier.

DR. MALLORY: The great problem in these peculiar bone conditions is to establish a diagnosis by any means, and the question may well be raised whether the x-ray or histologic diagnosis is more reliable.

CLINICAL DIAGNOSIS

Bone cyst, with pathologic fracture.

DR. ALBRIGHT'S DIAGNOSIS

Paget's disease of bone.

ANATOMICAL DIAGNOSIS

Fibrocystic disease of bone.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient was operated on by Dr. Henry C. Marble, who opened into what he believed to be a characteristic bone cyst. He curetted out a considerable amount of soft, gritty material. This was seen by several pathologists, one of whom said it was Paget's disease, but later retracted this diagnosis; one said it was fibrous dys-

plasia of bone; one could make nothing out of it but callus and repair. The cyst was packed with bone chips, and the patient made a fair recovery, went back to work and was quite well for a six-year interval. He then had another pathologic fracture and came in again. More x-ray films were taken on this entry, which Dr. Holmes will now show.

DR. HOLMES: They are poor films, and I cannot make much out of them. They are all taken through plaster and are overexposed.

DR. MALLORY: But there is no doubt about the fracture at that time.

DR HOLMES: No; it is nice to have one thing about which we are certain.

DR. MALLORY: On the second occasion the bone was explored, and again, a cyst was reported by the surgeon. Once more the gritty material was curetted out, and again, the cavity was packed with bone chips. On this occasion Dr. Castleman considered very strongly the possibility of sarcoma. I disagreed, as did Dr. Granville A. Bennett and Dr. Henry L. Jaffe, to whom we sent the sections. Dr. Bennett having seen these sections and having reviewed the first ones is now convinced that the diagnosis of Paget's disease was erroneous. He is inclined to think that it is a fibrocystic process, whatever that may be. Dr. Jaffe thinks the most probable diagnosis is bone cyst. No one is willing to support Paget's disease.

DR. WILLIAM B. BREED: What do you think it is?

DR. MALLORY: I would like to make it fibrous dysplasia.

DR. ALBRIGHT: Paget's disease is both fibrous and dysplastic. I will grant you that.

DR. MALLORY: Would one in a case of Paget's disease find gross bone cysts filled with fluid? The description that the surgeon has given us is rather inadequate. I confess the fragments that we received following the curettage give little idea of the gross pathology. We have some good sections for histologic examination, however, and they do not look like Paget's disease.

DR. ALBRIGHT: An x-ray man calls any circumscribed bone lesion without calcium a cyst. Pathologists have to have fluid to call it a cyst, whereas a surgeon calls any fibrous tissue a cyst.

DR. MALLORY: Our sections showed mostly fibrous tissue and spicules of osteoid, with multiple very small cysts scattered through the tissue.

DR. ALBRIGHT: I should have to see it under the microscope. Have x-ray films of the bones of the forearm been repeated?

DR. MALLORY: No. The diagnosis I have to make is fibrocystic disease of bone. It certainly does not look like Paget's disease.

DR. HOLMES: If you look at the case from this angle, it is apparent that everyone disagreed except the radiologists and Dr. Albright. You obtained different opinions from several pathologists, so I think the diagnosis is Paget's disease. The majority rules!

DR. MALLORY: This is a very satisfactory case for the clinicians because we cannot prove they are wrong.

DR. ALBRIGHT: I should still like to see the lesion in the radius.

* * *

DR. ALBRIGHT (subsequent note): It has occurred to me that the biopsies were all taken at the site of the fractures. I think this explains why the typical mosaic structure of Paget's disease was not found. The mosaic structure, of course, is the one distinguishing feature between Paget's disease on the one hand, and osteitis fibrosa localisata (bone cyst) and osteitis fibrosa disseminata on the other. I also looked up this patient and had his serum phosphatase determined on November 6, 1942, two months after the fracture. It was 12.5 Bodansky units per 100 cc. I therefore think we must attribute the high phosphatase to the underlying Paget's disease and not to the fracture.

CASE 29032

PRESENTATION OF CASE

A sixty-year-old widowed telephone operator was admitted to the hospital because of convulsions and loss of consciousness of two hours' duration.

The patient was in good health until two or three weeks before entry, when she developed persistent, vague nausea and epigastric cramps. During this time she lost about 10 pounds in weight. Four hours before entry, when she was aroused from sleep to eat supper and go to her usual night work, she complained of numbness of the hands. It was noted that her head was deviated to the right and that she seemed preoccupied. An hour later, she suddenly fell off her chair and had a generalized convulsion, lasting about seven minutes, in the course of which she lost consciousness, frothed at the mouth, bit her tongue and was incontinent. She remained unconscious and had two more convulsions, which were similar to the first although more severe. A physician gave an injection of "morphine," pried a spoon into the patient's mouth and referred her to the hospital.

The family history was negative. Many years previously the patient was refused life insurance because of a heart murmur, but she was subsequently accepted. About twenty years before entry she was thought to have had "stomach ulcers."

She had had an uneventful menopause a year before entry.

In the two hours following admission the patient was unconscious. Her jaws remained firmly clenched on a mouth gag, and her head was turned toward the right. The extremities were motionless, except during two convulsions, the first left sided and the second generalized. There was incontinence of urine. In the next hour the patient recovered consciousness sufficiently to answer questions. During this time the left arm and leg were completely flaccid, with positive Hoffmann and Babinski reflexes. Tendon reflexes were exaggerated in the left leg. The neck was somewhat resistant to flexion. There was left-sided facial weakness of the central type. In the next half hour or hour the patient became mentally clear except for slight disorientation, and was able to converse freely. The signs of left facial paralysis disappeared, and the patient was able to move the left arm and leg. There was a suggestion of grasp reflex in the left hand, but other abnormal reflexes were no longer present. The fundi were negative, and the external ocular movements and papillary reactions normal. The tongue was bruised and lacerated, and could be protruded in the midline. The neck was no longer stiff. The lung fields were clear. The heart was enlarged slightly to the left. The heart sounds were of good quality, with a systolic murmur audible all over the precordium. A cardiac consultant made a diagnosis of moderate aortic regurgitation. The abdomen was obese, with no palpable masses. The pelvis was essentially normal.

The blood pressure was 170 systolic, 80 diastolic. The temperature was 100.5°F., the pulse 115, and the respirations 22.

Examination of the blood showed a red-cell count of 4,570,000, and a white-cell count of 11,900 with 92 per cent polymorphonuclears. The urine showed a +++ test for albumin. The blood Hinton reaction was negative. The nonprotein nitrogen was 26 mg. per 100 cc. An electrocardiogram showed unusually high P and T waves, but seemed within normal limits.

A lumbar puncture during the middle period of semiconsciousness gave clear colorless fluid under an initial pressure of 250 mm., with normal dynamics; it contained 237 red cells per cubic millimeter and gave a + test with ammonium sulfate. The total protein was 246 mg. per 100 cc.; the gold-sol curve was 5555555554. The spinal-fluid Wassermann reaction was unsatisfactory in one examination and anticomplementary in another.

A roentgenogram of the skull showed marked bilateral thickening of the inner table of the frontal bone. There were no other unusual areas of calcification. The posterior clinoid processes were decalcified. The sella was not enlarged.

There was evidence of a left homonymous hemianopsia on the morning after admission, but two days later the visual fields were normal. The patient remained slightly dazed. The temperature remained about 100°F. On the fifth hospital day the patient developed a stiff neck and had a series of convulsions that could not be controlled by luminal or rectal ether. After this, she passed into progressively deepening coma, and died on the eighth hospital day without regaining consciousness. There was terminal rise in temperature to 105°F.

Differential Diagnosis

Dr. Henry R. Viets: The past history does not disclose any definite disease. The heart murmur that she had many years previously and that caused her to be turned down by a life-insurance company, although later accepted, can only be put down as a possible indication of valvular disease. The history of so-called "stomach ulcers" is even more vague. We have a note, moreover, that she was in good health a few weeks before the onset of her illness, and we know that she was working nights as a telephone operator even though her age was sixty. These facts would lead me to believe that she must have been in more than average health.

She developed persistent although vague nausea and epigastric cramps two or three weeks before the sudden onset of her epileptic attack. She had also lost 10 pounds in weight. These symptoms are not particularly suggestive of intracranial disease although they may denote some interference with the vagus nerves. Her weight is not given, but she is described as obese. This fact leads us to minimize the loss of 10 pounds. In a patient of slight weight, such a loss would be of much more importance.

We now come to the actual onset of a rather remarkable train of symptoms. The first symptom in the present illness was numbness of the hands. This was followed by some mental confusion or at least something that is described as a preoccupied condition with a deviation of the head to the right. The numbness of the hands is not particularly suggestive from the diagnostic point of view; the turning of the head to the right might indicate a spasm of the left sternomastoid muscle, and the preoccupation some vague mental state. After an hour she suddenly developed a generalized convulsion of severe degree, for it exhibited all the signs of marked epilepsy including loss of consciousness, frothing at the mouth, biting of the tongue and incontinence, as well as a sudden fall

off a chair. This was followed, moreover, within an hour or two by two more similar but even more severe convulsions, a condition of status epilepticus indicating a severe degree of cerebral dysfunction. Even after the patient entered the hospital she was unconscious and her masseter muscles were in spasm, with her head turned to the right. The convulsions continued, and then for the first time it is noted that one of them was on the left side of the body, thus corresponding with the turning of the head to the right, which was one of the earliest symptoms. Within an hour she recovered consciousness enough to answer questions. The whole episode of status epilepticus lasted six hours punctuated by various seizures. These left her with a left hemiplegia of the usual flaccid type, thus indicating the severity of the lesion, and with the ordinary positive Hoffmann and Babinski reflexes. For the first time it was noted that the neck was rather stiff, suggesting the presence of some foreign substance in the cerebrospinal fluid, probably hemorrhage.

Slowly the patient recovered consciousness and the paralysis disappeared, leaving her with a grasp reflex for a time, a common temporary residual of hemiplegia. The examination could then be made more in detail, and it was found that the pupils reacted normally and that there was no paralysis of the extraocular muscles or signs of choked discs. The neck, too, was no longer stiff; but we are not informed when this was discovered, and it is therefore difficult to say whether the absence of stiffness was subsequent to the lumbar puncture. We know that fluid was withdrawn at some time, but there again the timing is vague for it only states the "middle period of semiconsciousness." We presume this was on the evening of her illness, but the tap may have been performed later. The pressure was moderately increased, and there were over 200 red cells — whether they were crenated is not disclosed in the record. The total protein was ten times normal, and the gold-sol curve markedly affected. In spite of the fact that the fluid was colorless, there is every indication that considerable blood had appeared in the subarachnoid space some time prior to the puncture. It is important to know exactly when the puncture took place, for its timing is as valuable as the findings disclosed by examination of the sample. The Wassermann reactions were unsatisfactory, presumably because of the blood in the fluid. The other laboratory reports are not particularly helpful. A large amount of albumin in the urine is often found in cases of hemorrhage in the nervous system, particularly those of the subarachnoid variety. So far as I know this has not been explained. The low nonprotein nitrogen tends to rule out any chronic kidney condition. General examination showed moderate enlargement of the heart, with slight signs of aortic regurgitation. The electrocardiogram, too, was within normal limits, and I cannot see that the roentgenogram was helpful. The left homonymous hemianopsia is part of the left hemiplegia, only sensory rather than motor, and I presume that at the height of the left-sided motor paralysis there probably was a left hemianesthesia. This would be impossible to test for in her condition of semicoma.

The patient did fairly well in the hospital for three or four days, although always somewhat mentally confused. The signs of hemiplegia and hemianopsia disappeared. On the fifth day she again developed a stiff neck, indicating a fresh outpouring of blood into the subarachnoid space. This was followed by another series of convulsions. Subsequently coma developed, and the patient died on the eighth hospital day without regaining consciousness. There was a terminal rise of temperature.

The sudden onset of severe epilepsy leading to cerebral attacks can only indicate a severe intracranial lesion. We have evidence, on account of the left hemiplegia, that at least the major portion of the lesion was on the right side of the brain. This was confirmed, moreover, by the later discovery of homonymous hemianopsia. Sudden epilepsy is most likely due to cerebral thrombosis, although it may be the result of cerebral hemorrhage, particularly if the hemorrhage is cortical or meningeal. The slow onset of this patient's condition in which she had symptoms at least an hour before the generalized convulsion, is strongly suggestive of thrombosis rather than of hemorrhage. Although theoretically we assume that thrombosis is more likely than hemorrhage, we have the definite fact that there was blood in the spinal fluid. The bleeding, moreover, was sufficient to cause some stiffness of the neck even on entry to the hospital. Subsequently the spinal fluid was indicative of a condition in which blood must have been present in large amounts at one time. This is the only way one can account for the increase in total protein to nearly ten times normal and the marked change in the gold-sol reaction. Although the red-cell count was only 237 at the time the tap was made, one has every justification in assuming that many more cells were in the fluid at some previous time, perhaps sufficient to make the fluid red in color. That the initial lesion was hemorrhagic in nature and subsequently bled again is indicated by the finding of stiffness of the neck and convulsions on the fifth hospital day. We thus may assume, I think, that a hemorrhagic lesion of some

sort was sufficient to cause the symptoms. Was this hemorrhage primarily in the subarachnoid space or within the cerebrum itself?

The transient nature of the hemiplegia and the homonymous hemianopsia suggest that whatever lesion in the right side of the brain caused these two findings, was far from permanent. This is, therefore, not suggestive of a thrombosis or of an intracerebral hemorrhage. A surface hemorrhage, however, would give such findings, for the pressure might rapidly be adjusted. Such a hemorrhage, moreover, would account for the cortical irritation giving rise to the status epilepticus. Although a thrombosis in general gives rise to epilepsy more frequent than does hemorrhage, that comparison is usually made with intracapsular hemorrhage and not with meningeal hemorrhage, which is in evidence here.

Embolism seems even more unlikely. In the first place, the history of heart disease is vague and even the examination disclosed only a moderate lesion that was not suggestive of activity. To be sure an aortic valvular lesion may lie dormant and subsequently a portion may come away and act as an embolus. This would not in all likelihood account for the hemorrhage into the subarachnoid space, and most cardiac emboli that enter the brain do so on the left side and give rise to right hemiplegia with its accompanying aphasia. Embolic lesions, moreover, are likely to be more fixed and not so transient in nature. I therefore believe that, although we may find evidence of cardiac disease, such as an aortic lesion, it is not likely that this lesion was the cause of death, even in a secondary manner through cerebral embolism.

Finally, we have to consider the likelihood of an aneurysm as the etiology of the subarachnoid hemorrhage. The onset of the illness is not quite so prompt as we find in most cases of bleeding aneurysm. We have, however, plenty of evidence that aneurysms may leak slowly and sometimes give symptoms for two or three weeks in advance of their rupture, such as might well have occurred in this case. The bleeding at the time of rupture may be sufficient to give a generalized convulsion. Apparently more blood appeared on the right side than on the left, and therefore the generalized convulsions were mixed with left-sided attacks. This condition quieted down; but after five days it was resumed in the hospital, and in three days death ensued. There is no indication where such an aneurysm arose. We must think of the usual position of these lesions in the circle of Willis, but in this case there is nothing to give us a lead concerning what part of the circle was affected.

We might be dealing, of course, with bleeding from some lesion other than aneurysm. Occasionally we find symptomless gliomas that disclose themselves by bleeding. That is a possibility but a rare one. There are also vascular tumors such as hemangiomas, long quiescent, that suddenly announce themselves by bleeding into the subarachnoid space or into the brain. These lesions are rare, and although they are possibilities, in this case I do not believe we can make either diagnosis.

The diagnosis, therefore, is cerebral hemorrhage, possibly subarachnoid in type, more on the right side than the left. Aneurysm of a cerebral vessel is a strong possibility, with location not disclosed.

DR. EARLE M. CHAPMAN: Did you say that embolism in heart disease was statistically commoner on the left side of the brain than on the right?

DR. VIETS: Yes; I think that is right.

DR. JOST MICHELSEN: Do you think the combination of aortic regurgitation, the high protein in the cerebrospinal fluid and the gold-sol curve suggests a syphilitic lesion?

DR. VIETS: A gold-sol curve with so many 5's in it always indicates that there has been blood in the spinal fluid. That is the only thing I know of that can give a gold-sol curve like this one. The high protein also means that there must have been some blood in the fluid. Whether that came from a vascular lesion other than aneurysm or hemangioma, I do not see how we can tell. There is no history up to the present illness that indicates that the patient had a hemangioma. She had no cerebral symptoms.

DR. MICHELSEN: If hemorrhage accounted for the high protein, would they not have seen a discoloration of the spinal fluid?

DR. VIETS: That is why I was interested in when the cerebral spinal fluid was examined.

DR. CHARLES S. KUBIK: It was done on the day after the patient was admitted.

DR. VIETS: That seems almost too soon for color to appear in the spinal fluid. A little yellow tinge I am quite sure is missed very frequently. If it is bright red anyone sees it.

DR. G. COLKET CANER: The facts that she lost 10 pounds in weight and had nausea and epigastric cramps, then woke up complaining of numbness of both hands give a vague impression of multiple lesions. Those things, together with the fact that she had a little blood and a high protein in her spinal fluid, indicating previous hemorrhage, make one think of the possibility of metastatic disease. There is not much evidence of it here, but there is a slight indication of multiple lesions.

DR. KUBIK: When I saw the patient I was impressed by the stiff neck and the red cells in the spinal fluid, thought of subarachnoid hemorrhage, wondered about the possibility of aneurysm but

ended up by saying that nothing I could think of fitted the picture very well. The important thing, it seemed to me, was to control the seizures, using ether anesthesia if necessary. Status epilepticus, regardless of the underlying condition, is likely to result in death, apparently from pulmonary congestion and edema. The ether should be given by inhalation.

Dr. Paul D. White saw the patient, and said:

> A moderate amount of aortic regurgitation, dating back evidently fifteen years and therefore doubtless rheumatic in origin, is the only clear-cut finding on physical examination. This lesion is a good background for subacute bacterial endocarditis, of which, however, there is as yet no other evidence.

Red cells in the spinal fluid are often observed with cerebral complications of subacute bacterial endocarditis.

In view of what was found on post-mortem examination I am surprised that there were no white cells in the spinal fluid. I think that there must have been white cells.

Dr. Viets: Of course that would change the picture a good deal.

Clinical Diagnoses

Cerebral hemorrhage.
Aortic regurgitation.
Bronchopneumonia.

Dr. Viets's Diagnosis

Cerebral hemorrhage, possibly subarachnoid (? aneurysm of cerebral vessel).

Anatomical Diagnoses

Neurosyphilis, meningovascular.
Syphilitic aortitis, with aneurysm.
Cardiac hypertrophy.
Pulmonary edema and congestion, slight.
Frontal hyperostosis.
Fibroid tumors of uterus.

Pathological Discussion

Dr. Tracy B. Mallory: Will you tell us about the cerebral findings at autopsy, Dr. Kubik?

Dr. Kubik: There was no hemorrhage, no evidence of bleeding anywhere, either on the surface or within the substance of the brain, and no arterial occlusion or softening. There was one clue—a roughening of the ependyma of the floor of the fourth ventricle that was a little different from the usual so-called "granular ependymitis." This suggested neurosyphilis as a likely possibility, and the diagnosis was confirmed by microscopic sections.

There was an exudate of lymphocytes and plasma cells in the subarachnoid space over the brain stem and cerebral hemispheres. In the cerebral cortex and also in the cerebellum there were scattered areas in which there was extensive perivascular infiltration with lymphocytes and plasma cells, nerve-cell degeneration and gliosis. No doubt there were many other areas like that. Some of these vessels were occluded. In other parts the cortex did not look very abnormal. There was an endarteritis of the medium-sized arteries in the subarachnoid space of the brain stem. I am not sure whether the diagnosis is general paresis or meningovascular syphilis but favor the former for the cortical pathology.

Dr. Mallory: On examination of the cardiovascular system we found confirmatory evidence for the diagnosis of syphilis. The aortic valve showed a distinct separation of the cusps at the commissures, and the coronary arteries appeared to take their origin 2 or 3 mm. above the upper margin of the aortic cusps, thereby indicating that attachment of the cusp had gradually been lowered, as it so characteristically is in syphilitic involvement of the aortic valve. The ascending aorta was moderately dilated and showed a great deal of wrinkling. On microscopic examination there were focal destruction of the media and perivascular infiltration of lymphocytes in the adventitia and also in the vascularized media. I think that both the cerebral and vascular findings are characteristic enough to permit us to make a positive diagnosis even without serologic support. There was a slight pulmonary congestion and edema, secondary, I believe, to the status epilepticus. A coincidental lesion was hyperostosis of the frontal bones; I do not believe it played any part in the symptomatology.

Dr. Chapman: Did you do a Hinton test on the blood obtained at autopsy?

Dr. Mallory: No; such tests are usually not very satisfactory, since they are likely to give anticomplementary reactions.

Dr. Viets: Do you want to comment on status epilepticus as the terminal event in a general paretic?

Dr. Kubik: I think that a patient may die of status epilepticus quite apart from the underlying disease, which may be neurosyphilis, brain tumor or something else. Every effort should be made to stop the convulsive seizures and to do so as quickly as possible. The usual anticonvulsive drugs often have little or no effect on the convulsions, and when given in large doses, may do considerable harm. Ether anesthesia, in my experience, has been very effective, and I believe that it is also less harmful. It acts quickly and surely and is rapidly eliminated.

I should suppose that in the present case the patient died as a result of status epilepticus, with pulmonary congestion and edema as the chief cause of death.

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PRESIDENT-EMERITUS LOWELL AND MEDICAL EDUCATION

The late A. Lawrence Lowell, president-emeritus of Harvard University, always took a great interest in the Harvard Medical School. In June, 1939, he made some informal remarks on medical education to the Class of 1914 on its twenty-fifth anniversary. These remarks were subsequently published in the March 21, 1940, issue of the *Journal* and were commented on editorially in the same issue. This article reflects his considered opinion regarding the education of physicians.

Mr. Lowell always maintained that it was unwise to argue with an expert on the expert's own ground. Consequently, his contributions on medical education were by way of suggestions rather than by declared policies. Mr. Eliot used the phrase, "prodigious advances in medical science," whereas Mr. Lowell referred to the "vast improvement in medical education." Perhaps Mr. Lowell's most concrete suggestion was the introduction of general examinations at the Harvard Medical School in 1914. These were largely based on the type of examination then employed at Harvard College.

Mr. Lowell was always distressed by the length of medical education. He once referred whimsically to the possibility that a man would be forced to retire on account of age just before he completed his training. He had the feeling that there were needless attempts to cover too much ground and that, of necessity, much of the material was forgotten by the student before he had any opportunity to put it to use. He claimed that there was a tendency to add the new to the old without sufficient effort to eliminate some things no longer needed, and believed that it should be possible to solidify and simplify the curriculum, in which he included the time spent in hospitals.

He was always very fond of the following anecdote. His brother once complained bitterly to his father, "Doctors really know very little." His father replied, "Yes, that is true, but the doctors know a little more than we do and so we find them valuable." Mr. Lowell would then go on to say that he had seen the situation entirely changed and that such a remark would not be appropriate today. He added, however, that the change, unfortunately, seemed to have been made at the cost of the withdrawal, as compared with former times, of the medical profession from civic affairs, to which they could contribute so much.

THE PERIOD OF RESISTANCE

Many children — indeed it would be safe to say nearly all children — some time in their early, preschool years of life, enter a period of stubbornness, contrariness and spitefulness that, if improperly handled, may miscolor the rest of the stages of their lives and set a pattern for their maturer

years. By no means all children constitute serious problems at this period, but it is fair to say that any child worth the raising constitutes somewhat of a problem.

This period has for years been called the "neglected age" of childhood, the cause of the neglect lying quite reasonably in the attitude of the child toward interference with his independent desires; Benjamin,* whose studies at Johns Hopkins University represent the most recent contribution to the problem, calls it the "period of resistance."

Underlying the spite and negativism that make up the chief characteristics of this period, with their varying expressions of misbehavior from thumb-sucking to bed-wetting, from temper tantrums to encopresis and head-rocking, is always a basis of anxiety or inner insecurity — the result of an unsuccessful transition from infancy to early childhood. All human personality difficulties stem from a combination of hereditary and environmental factors, as the architecture of any building must be determined by the type of building materials available, as well as the skill of the architect. With due allowance for the material utilized, these poor results are obtained from a training that does not give enough independence, or destroys self-confidence by punishment and frustration.

Benjamin's plea is for a family structure that recognizes the rights of all its members from the beginning. He writes:

> Real democracy begins at the beginning, when neither parental nor infantile despotism should be allowed to govern the social unit which is the home. Disturbing rebellion, which is still so frequent in children . . . has no opportunity to flourish in an atmosphere of good sportsmanship, reasonable compromise, reciprocity and mutuality.
>
> Unwholesome remonstrance can be prevented. Such an attitude is over and above the safest guarantee for the rearing of self-dependent, conforming, considerate, truly free and democratic Americans.

Undoubtedly, a fuller appreciation of this precarious period in early childhood by both physicians and parents will do much to prevent many of the difficulties that arise in later life.

*Benjamin, E. The period of resistance in early childhood. *Am. J. Dis. Child.* 63:1019-1077, 1942.

MEDICAL EPONYM

Sprengel's Deformity

Otto Sprengel (1852–1915), chief surgeon at the Children's Hospital of Dresden, described "Die angeborene Verschiebung des Schulterblattes nach oben [Congenital Upward Displacement of the Shoulder Blade]" in the *Archiv fur klinische Chirurgie* (42: 545–549, 1891). A portion of the translation follows:

> During the past year I have had the opportunity, four times in all, to observe a deformity of the shoulder blade in children of different ages, which, in the absence of any effective extrauterine causes, must be considered congenital. . . . This may be briefly characterized as follows: One shoulder blade (the left) lies about 2 or 3 centimeters higher than the other, without any other demonstrable anomaly of the back or thorax. . . . The fact that in the observed cases it was always the left shoulder blade which showed this anomalous position must be considered a matter of chance.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SOCIETY HEADQUARTERS

Owing to the decreased supply of fuel oil, the Boston Medical Library will continue to be closed on Saturday and will be open from Monday through Friday from nine in the morning to three in the afternoon, until further notice. The headquarters of the Society and the offices of the *Journal* will be closed to conform with this schedule. In an emergency, the officers of the Society and the managing editor and associate editors of the *Journal* can be located through their other offices or homes.

SECRETARY'S OFFICE

The following letter is published for the information of members of the Society:

Michael A. Tighe, *Secretary*

• • •

Dear Dr. Tighe:

The Office of the Surgeon General has informed me that the United States Public Health Service is in need of an average of twenty-five physicians per month for Coast Guard and War Shipping Administration work, and others for the States Relations Division and miscellaneous assignments.

These physicians will be commissioned in the United States Public Health Service Reserve in the grade of assistant surgeon, or passed assistant surgeon if over thirty-

three years of age. Application forms will be available at this office.

It will be appreciated if you will bring this matter to the attention of your members or affiliates and urge any who are interested to communicate with me.

Sincerely yours,

R. P. Sandidge, *Senior Surgeon*
Medical Officer in Charge

United States Marine Hospital
Boston

COMMITTEE ON MATERNAL WELFARE

Analysis of Causes of Maternal Death in Massachusetts during 1941

Miscellaneous

Of the 5 cases of ruptured uterus that occurred during 1941, the first was that of a thirty-four-year-old woman who had had no prenatal care during this pregnancy and whose history does not relate whether there had been any previous pregnancies. She was first seen at home as an emergency because of profuse vaginal hemorrhage when about five months pregnant and immediately taken to the hospital by ambulance. Bleeding did not recur. X-ray films taken four days after admission revealed no evidence of fetal bones. Three days later a curettage was performed, the pathological diagnosis of which was "degenerative decidual tissue and hyperplastic endometrium." The patient's temperature rose immediately after the curettage; two days later the abdomen became distended, and death occurred the following day. Autopsy showed peritonitis, with rupture of the uterus on the right, the opening being just large enough to admit the passage of a No. 3 dilator. A macerated fetus of five months, with the placenta, was found in the right lower quadrant. The rupture of the uterus was probably traumatic. It is very likely that the pregnancy was abdominal, since it is inconceivable that the fetus and the placenta could have passed into the abdominal cavity through so small a rupture in the uterus. The diagnosis was undoubtedly missed; if the proper diagnosis had been made when the patient was first seen, and a laparotomy performed, this catastrophe could probably have been prevented.

The second patient, a thirty-one-year-old woman who had had one previous miscarriage, first consulted her physician when about four months pregnant; she complained of pain in the shoulder, and several hours later went into profound shock. The diagnosis of ruptured ectopic pregnancy was made, and the patient was sent to the hospital, arriving pulseless and without a demonstrable blood pressure; death occurred very shortly thereafter. Autopsy showed rupture of the uterus, with a four-month-old fetus still in the sac and a placenta accreta. The patient's past history was negative, except for the previous miscarriage when three months pregnant. Spontaneous rupture during the fourth month of pregnancy is a most unusual occurrence. It is possible that if the proper diagnosis had been made when the patient was first seen, before she went into shock, abdominal operation would have been successful.

The third patient, a forty-year-old para II who had had excellent prenatal care, went into labor at term. She had very severe pain during labor and was delivered normally ten minutes after admission to the hospital. The baby was dead, and an excessive hemorrhage followed delivery. The patient became pulseless and went into shock, and died ten minutes after delivery of the placenta. Autopsy proved the cervix to be torn deep into one vault, the tear extending into the uterus and broad ligament; the uterine artery on the right was severed. There is no note that pituitrin had been used, and it is possible that the cervix was so filled with scar tissue from the previous delivery that the tear into the broad ligament resulted from the rupture of undilatable scar tissue. This was an unfortunate case but one in which in all honesty the blame cannot be laid to inadequate or overzealous obstetrics.

The fourth case occurred in a thirty-six-year-old patient who had had a previous cesarean section for placenta previa. When about thirty-six weeks pregnant she complained of severe abdominal pain and was immediately sent to the hospital. A general surgeon was called as consultant, and ¼ gr. of morphine was ordered. The patient died undelivered two hours later, autopsy showing that the uterus had ruptured along the scar of the previous section. The baby was lying in the abdominal cavity. There was no excuse whatever for this fatality. One quarter of a grain of morphine has never saved the life of a patient with a ruptured uterus.

The fifth patient, a thirty-eight-year-old primipara who was delivered at term by low forceps, had a severe post-partum hemorrhage; examination revealed an incomplete rupture of the uterus. Supravaginal hysterectomy was performed, and the patient was transfused four times. The signs and symptoms of peritonitis developed thirty-six hours post partum, and the patient died of peritonitis on the fourth day. Rarely, the cervix does rupture in a normal delivery and does cause profuse post-partum hemorrhage. From the record one would infer that the operation was not difficult, and hence not the cause of the rupture. Everything possible in the way of treatment was done for this patient: a specific diagnosis was made, the patient was

transfused four times, and the uterus was removed. It is lamentable that infection developed.

In these 5 cases of ruptured uterus, it is gratifying that none were the direct result of overzealous operating and that autopsies were performed in all but a single case.

Of the 2 cases of inverted uterus, the first occurred in a thirty-six-year-old multipara who had had adequate and intelligent prenatal care and was delivered normally after a six-hour labor. The placenta and membranes were delivered spontaneously forty-five minutes after the baby, along with the inverted uterus. The placenta was lightly adherent to the uterine wall and was removed. Attempts to replace the uterus, consuming two hours, were unsuccessful, and profuse hemorrhage was constant. Death occurred during the laparotomy that was performed for the purpose of reducing the inversion. The patient was transfused. There is no evidence in the record that undue effort was made to stimulate separation of the placenta. It is unfortunate that so much time was lost in an unsuccessful attempt to replace the fundus, and this must be regarded as an avoidable death.

The second patient was a twenty-two-year-old woman in her second pregnancy who had been seen from the sixth month by her physician and was delivered normally at term. The uterus, however, became inverted after the placenta was delivered, and the patient went into profound shock. Attempts to replace the uterus were at first unsuccessful, but a consultant did so with no difficulty. In spite of transfusion, the patient did not rally from the shock and hemorrhage and died shortly after delivery. Without question the delay in replacing the uterus, during which time hemorrhage continued, was the cause of this fatality.

The 1 case of abdominal pregnancy occurred in a thirty-three-year-old patient who had had two previous pregnancies and was not seen in her third pregnancy until she was sent to the hospital. A mass was palpated in the posterior cul-de-sac; this was aspirated and blood obtained. Laparotomy was immediately performed, and a four-month-old fetus was found in the abdominal cavity, with the placenta attached to the broad ligament. There was free blood in the abdomen. The fetus and part of the placenta were removed. The broad ligament at the site of the attached placenta was packed. Death occurred shortly after the operation and before a transfusion could be administered. It has long been recognized that the placenta in an abdominal pregnancy should be left in situ. Gauze packing placed against the placenta itself and left there, allowing the placenta to separate slowly, has proved the safest procedure. Attempts to remove the placenta at the time of operation too often result in uncontrollable hemorrhage. Had no attempt been made to remove the placenta manually in this case, and had the packing been put at the site of the placenta, it is possible that this fatality would have been averted.

REPORT OF MEETING

NEW ENGLAND PATHOLOGICAL SOCIETY

A meeting of the New England Pathological Society was held at the Deaconess Hospital on the evening of October 15.

The first paper was "Tumors of Cutaneous Glands," by Dr. Olive Gates. The study showed that these tumors rise from all the cutaneous glands and that the importance of their recognition depends on an apparent peculiarity of behavior differentiating them from the commoner epidermoid and basal-cell carcinomas, with which they are often confused. A large proportion of the benign forms are congenital, and many of the carcinomas develop from these benign tumors. Neoplasm is commoner in the sweat gland, and may conform to the generalized type and the modified forms — apocrine, ciliary and ceruminous. The tumors of the sebaceous glands are less well understood. There is no uniformity of opinion concerning the status of benign enlargement of these glands, and the carcinomas have been overlooked. Histologic differentiation of hypertrophy and adenoma is difficult. Expansile, discrete enlargement of the sebaceous gland is properly classed as adenoma. Carcinoma of this gland is probably more frequent than the literature indicates. In a discussion of the paper it was brought out that, as a rule, tumors of sweat glands are radioresistant.

The second paper was on the subject, "Nonepithelial Tumors of the Stomach," by Dr. William A. Meissner. This study was confined to a determination of the incidence of leiomyomas. In a series of 30 autopsies chosen at random, careful gross and microscopic examination, with particular emphasis on careful palpation of the gastric wall, showed a total of twenty-nine leiomyomas in 15 cases. These tumors were slightly commoner in males, were found in the age group from fifty to eighty years and were most frequent in the fundus. For the most part there was no associated gastric pathology. In the discussion it was brought out by Dr. Shields Warren that the fact that the incidence of this type of tumor was higher in the stomach than in the uterus places a questionable value of the theory of endocrine relation to its origin. He also stressed the value of careful palpation in finding small tumors of this type. Dr. Orville T. Bailey brought out the point that clinical cases with erosion of the overlying mucosa and hemorrhage have occasionally been diagnosed by their rather characteristic x-ray appearance.

The next paper was "Interstitial Cell Growths of the Testicle," by Dr. Kenneth W. Olshausen. The author proposed a classification of hyperplasia, local tumor and malignant tumor. On the basis of 24 cases from the literature and 4 personal cases, the definition of hyperplasia was an increase of interstitial cells between the seminiferous tubules without destruction or displacement of the tubules beyond the limits of the tumor; of these there were 12 cases. The characteristics of the local tumor group

were discrete nodules or groups of interstitial cells locally replacing or displacing the seminiferous tubules. Of these there were 13 cases. There were only 3 cases of malignant tumor, which is regarded as an increase of interstitial cells with anaplasia, destruction of tubules and metaplasia. The main features distinguishing these groups are the number and pattern of distribution of the cells. The histologic characteristics, except in the case of malignant tumors with metastases, do not offer enough variation to distinguish between the various types of growth in the presence of the meager clinical data available. Furthermore, there is no satisfactory method of determining the number of interstitial cells in the normal person, because of the variability in the number, size and distribution of the seminiferous tubules, blood vessels, nerves and connective-tissue cells. The "normal number" of interstitial cells is only a visual impression gained by microscopically comparing sections from a series of three hundred and seventy testicles obtained at autopsy and from surgical material. Hormonal changes were relatively few except in children in whom there was precocious puberty with gynecomastia. For the most part ketosteroid determinations were not done. However, in one case report by Mason, the Aschheim–Zondek test was positive in a 1:50 dilution.

The last paper was given by Dr. Shields Warren and was entitled "Bone-Marrow Changes following the Administration of Radioactive Phosphorus." The report was based on 8 patients who had come to autopsy a varying length of time following the administration of radioactive phosphorus, either orally or intravenously, as disodium phosphate. The changes induced in the bone marrow do not differ significantly from those seen in other types of radiation, such as deep x-ray therapy. The changes ranged from very marked depletion of the marrow with almost no abnormal cells and few normal cells to practically no changes, except for minor evidence of damage to cells of the granulocytic series and to some of the megakaryocytes. In most cases there was radiation effect in all marrow elements. As evidenced by examination of the peripheral blood and bone marrow, the general effect of radioactive phosphorus seems to be injury to all marrow elements, with particular effect on the more rapidly proliferating cells. These cases received small doses of low intensity, having been given 2 millicuries at ten-day intervals with the dose gradually spreading to once every three to six months. The phosphorus is taken up by the rapidly growing cells, and is accompanied by a drop of the total white-cell count, with a greater percentage of mature cells in the peripheral blood, and a decrease in the number of erythrocytes and platelets. If the dosage is sufficiently small, the effect may be selective on the leukemic cells. In summary, Dr. Warren said that the number of cases is not sufficient for clinical evaluation and that the advantages to date are of minor importance. The latter are as follows: there is no radiation sickness; it is easy to maintain the proper level by either oral or intravenous administration; and treatment can be carried out without bringing the patient to the hospital. It is also quite probable that the dose is concentrated at the point of disease. In the discussion it was brought out that in patients given large doses the effect on the marrow approaches that seen in aplastic anemia and that damaged cells, at least those showing evidence of vacuolization, are found in the circulating blood. Hemosiderin was found in rather abundant amounts, but the amount was not thought to have any clinical significance.

BOOK REVIEWS

Four Treatises of Theophrastus von Hohenheim, Called "Paracelsus." Translated from the original German, with introductory essays. By C. Lilian Temkin, George Rosen, Gregory Zilboorg, M.D. and Henry E. Sigerist, M.D. Edited, with a preface, by Henry E. Sigerist, M.D. 8°, cloth, 256 pp., with 1 portrait. Baltimore: The Johns Hopkins Press, 1941. $3.00.

The character of Paracelsus was full of contradictions, — violent ones, — which explains why to some he has seemed no better than a besotted charlatan and to others little short of a sainted mystic. The truth — as it so often does — lies in the middle ground. The force of his personality and the originality of his mind cannot be denied. He quarreled so violently and persistently with his professional colleagues that he became an habitual outcast, and many of his writings were denied publication during his lifetime. Yet, he was the founder of chemical therapeutics; he wrote the first treatise on industrial medicine, which discussed miners and their ailments; and he attempted something in the direction of psychiatry and psychology. For the whole list of his contributions, one should consult a book on medical history. All in all his was a great part, and worthy of recollection.

He died four centuries ago, and this book is essentially a memorial volume. The four treatises, each translated by a different hand, are as follows: *Seven Defensiones*, an attempt to justify his views of medicine in opposition to those then prevailing; *On the Miners' Sickness and Other Miners' Diseases*; *Diseases That Deprive Man of His Reason*; and *A Book on Nymphs, Sylphs, Pygmies, Salamanders* and so forth, which according to Professor Sigerist affords a good example of Paracelsus's philosophy and theology.

It is pleasant to have something besides hearsay about so important a man. But these treatises are not easy reading. There is much in them that seems obscure, but, as Professor Sigerist remarks in his preface, to translate Paracelsus into modern English would lose much of the original meaning. With all the difficulty, one can discern in the man a trait of shrewd medical observation and a pervading spirit of honesty of mind. And those facts alone are worth the learning.

Food and Beverage Analyses. By Milton A. Bridges, M.D., and Marjorie R. Mattice, M.S. Second edition, thoroughly revised. 8°, cloth, 344 pp., with 40 tables. Philadelphia: Lea & Febiger, 1942. $4.00.

This second edition, revised and amplified by Professor Mattice after the death of Dr. Bridges, is intended as a reference book for clinicians, students, dietitians, nurses and those concerned with applied nutrition and dietetics. It aims "to provide analytical data on the largest possible number of food factors . . . presented in a readily understandable fashion." The bulk of the material consists of tables of the composition of foods and beverages; but there are also brief general discussions, including chapters on carbohydrates, proteins, fats, water, vitamins, acidity of foods, inorganic salts and alcoholic beverages. There is a glossary of vitamin terms, including the structural formulas of some of the more important vitamins. An extensive bibliography is appended. The figures for food analyses are partly collected from reports in the literature and partly from the authors' own work. They are undoubtedly reliable and as free from error as is humanly possible.

There is great call for such a collection of readily available food and beverage data, attested to by the haziness in the minds of many clinicians concerning food values, and the general tendency to pass all diet-making along to the dietitian. There is also a need for periodic additions to the available data, to include foods and products that are constantly being introduced. Only a few recent single publications meet these needs, notably Chatfield and Adams's *Proximate Composition of American Food Materials* (United States Department of Agriculture Circular No. 549 — June, 1940) and the present volume, which is the more extensive.

Although knowledge of the exact composition of foods is most desirable, Bridges and Mattice are quick to point out that many, if not most, of the present analytical data are of necessity anything but exact. Naturally occurring foods vary widely in composition, and such factors as freshness, variable water content, differences in soils, processing and cooking make anything but average values impossible. Furthermore, there are varying factors in the absorption and utilization of some constituents. For example, if one eats spinach, which has a considerable calcium content but is also rich in oxalates, it not only supplies no available calcium but also makes unavailable much of the calcium in other foods ingested at the same time. Finally, there are technical difficulties in chemical analysis, and different workers report widely divergent figures for the same food factors. For example, the English workers, McCance, Widdowson and Shackleton, give figures for the crude-fiber content of foods that are consistently two to eight times higher than those of other workers.

Some data in these tables, although as accurate as possible, are of dubious applicability in dietetics. The acidity of foods as eaten, for example, has no relation to their final effect in body metabolism, as the authors note. Such tables could well be omitted.

If due account is taken of all these pitfalls in the figures, this volume will be of great value to everyone in the field of practical dietetics.

Clinical Hematology. By Maxwell M. Wintrobe, M.D., Ph.D. 8°, cloth, 792 pp., with 167 engravings and 7 colored plates. Philadelphia: Lea and Febiger, 1942. $10.00.

This book is by far the best English text on the subject of clinical hematology. Crowded into its pages is a wealth of material, all carefully annotated and documented, and replete with references. The completeness of these references — author, title, volume and page — is an indication of the care with which the entire book has been written, from introduction to index, and is confirmatory of the author's reputation as a careful investigator of hematologic and nutritional problems.

In the last few years a wealth of new hematologic texts in English has appeared to fill the large gap formerly present in this field. Some, like that of Kracke, have had excellent illustrations with a rather indifferent text; others, like that of Haden, have quite frankly been written for the general practitioner and as such have been rather elementary in their scope. The monumental four-volume "handbook," edited by Downey, is somewhat unbalanced by its editor's histologic bias, with the result that the clinical articles are often subordinated and given but scant attention. Wintrobe, being primarily a clinician with both physiologic and histologic training, has been able to keep the proper balance between these fields and has thus produced a first-rate work, which is difficult to criticize.

Descriptions of the blood-forming organs and of the blood cells are complete and free both from the unnecessary polemics regarding derivation of cells and the unique nomenclatures affected by both Osgood and Kracke. The chapter on macroscopic examination of the blood, including the various indices, is new for hematologic texts and reflects Wintrobe's pioneering efforts in this field. Anemia is first considered as a general physiologic problem, the matter of therapy receiving a 50-page section. In the chapters on the various specific diseases, two things stand out: the large number of references, — commonly seen only in monographic articles, — and the consideration of pathology and pathogenesis at the end of each chapter. Ordinarily, one would expect to find possible pathogenetic mechanisms first, pathology second, clinical features third, and treatment last. It must be conceded, however, that Wintrobe's arrangement detracts but little from the value of the book. The chapters on hemolytic anemia, sickle-cell anemia and Mediterranean anemia are excellent, far outranking similar chapters in other texts. Except for hypoprothrombinemia, the hemorrhagic diseases are well covered, as are the leukemias and leukocytic neoplasms. There is a brief but comprehensive chapter on the spleen.

In short, the reviewer has nothing but fulsome praise for Wintrobe's book. One might like a little less didacticism and a little more physiology here and there — but this is captious criticism.

Architectural Principles in Arthrodesis. By H. A. Brittain, M.A., M.Ch. With a foreword by Harry Platt, M.D., M.S., F.R.C.S., F.A.C.S. (hon.). 8°, cloth, 132 pp., with 144 illustrations. Baltimore: The Williams and Wilkins Company, 1942. $6.00.

In this small, superbly illustrated volume, an attempt is made to apply certain principles of architecture to the operation of arthrodesis. It is shown in drawings and photographs that stresses which may lead to failure in an attempted fusion of a joint can be combated by struts made from tibial grafts. The technic of applying such grafts to each joint during the operation of arthrodesis is described. The broad indications for arthrodesis that the author advocates, however, are not accepted in the United States. Here, arthrodesis, except in the case of tuberculosis, is used only as a last resort, but in the author's practice it is the primary operation in many disabilities. The majority of procedures appear to be sound, but the operations that the author performs for arthrodesis of the hip and the ankle seem to make the procedures unnecessarily long and difficult.

Hippocratic Medicine: Its spirit and method. By William A. Heidel. 8°, cloth, 149 pp. New York: Columbia University Press, 1941. $2.00.

In the days of Hippocrates, Greek medicine, as well as Greek science, was intimately tied in with philosophy. The most significant Hippocratic contribution was, in the last analysis, a point of view — but one so valid that, in essence, it still holds after two and a half millenniums. In this pleasant little book, Professor Heidel discusses the methods, the manners and the posture of medicine in the fifth century B.C. It is not a "must" book, of course, but to read it will be a pleasure and a profit to any physician with a feeling for history and a reverence for the ideals of his profession.

(Notices on page x)